THE AMERICAN JOURNAL OF PSYCHIATRY

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In this issue:

Second Messenger Systems and Psychoactive Drug Action: Focus on the Phosphoinositide System and Lithium

By Jay M. Baraban, Paul F. Worley, and Solomon H. Snyder

Erotomania Revisited: From Kraepelin to *DSM-III-R*

By Jonathan H. Segal

Simple Schizophrenia: Past, Present, and Future

By Donald W. Black and Todd J. Boffeli

Official Journal of the American Psychiatric Association

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References: 1. Rickels K, et al: Buspirone and diazepam in anxiety: A controlled study. *J Clin Psychiatry* 1982;43(12, Sec 2):81-86. **2.** Newton RE, et al: A review of the side effect profile of buspirone. *Am J Med* 1986;80(suppl 3B):17-21. **3.** Lucki I, et al: Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. **4.** Lader M: Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(suppl 5A):20-26.

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: *General*—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic eff
(ie, represent akathisia).

***Information for Patients*—**Patients should be instructed to inform their physician about any medicatio
prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with bu
spirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnan
while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

***Drug Interactions*—**Concomitant use with other CNS active drugs should be approached with caution (see
Warnings). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a fe
patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol co
centrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tight
bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firm
bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone wa
given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

***Carcinogenesis, Mutagenesis, Impairment of Fertility*—**No evidence of carcinogenic potential wa
observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromo
somal aberrations or abnormalities did not occur.

***Pregnancy: Teratogenic Effects*—**Pregnancy Category B: Should be used during pregnancy only
clearly needed.

***Nursing Mothers*—**Administration to nursing women should be avoided if clinically possible.

***Pediatric Use*—**The safety and effectiveness have not been determined in individuals below 18 years of

***Use in the Elderly*—**No unusual, adverse, age-related phenomena have been identified in elderly pati
receiving a total, modal daily dose of 15 mg.

***Use in Patients with Impaired Hepatic or Renal Function*—**Since buspirone is metabolized by
liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

***Associated with Discontinuation of Treatment*—**The more common events causing discontinuation in-

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The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness (12%), nausea (8%), headache (6%), nervousness (5%), lightheadedness (3%), and excitement (2%).

*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

cluded: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: *Signs and Symptoms*—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

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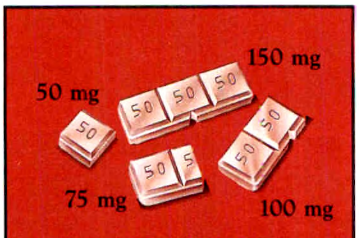

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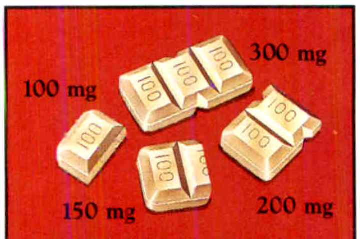

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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 146, Number 10 October 1989

EDITORIAL

1249 The Chronically Mentally Ill, Residency Training, and Psychiatry *Michael Alfred Peszke*

SPECIAL ARTICLES

1251 Second Messenger Systems and Psychoactive Drug Action: Focus on the Phosphoinositide System and Lithium *Jay M. Baraban, Paul F. Worley, and Solomon H. Snyder*

1261 Erotomania Revisited: From Kraepelin to *DSM-III-R* *Jonathan H. Segal*

1267 Simple Schizophrenia: Past, Present, and Future *Donald W. Black and Todd J. Boffeli*

REGULAR ARTICLES

1274 Cognitive-Behavioral Treatment of Depressed Inpatients: Six- and Twelve-Month Follow-Up *Ivan W. Miller, William H. Norman, and Gabor I. Keitner*

1280 Risk of Schizophrenia in Character Disordered Patients *Wayne S. Fenton and Thomas H. McGlashan*

1285 Study of 60 Patients With AIDS or AIDS-Related Complex Requiring Psychiatric Hospitalization *Jay W. Baer*

1289 Time Course of Antipsychotic Effects of Neuroleptic Drugs *Paul E. Keck, Jr., Bruce M. Cohen, Ross J. Baldessarini, and Susan L. McElroy*

1293 Defining and Measuring Stabilization of Patients During 4 Years of Intensive Community Support *Robert G. Wright, Julia R. Heiman, Jill Shupe, and Glenette Olvera*

1299 Panic Disorder and the Menstrual Cycle: Panic Disorder Patients, Healthy Control Subjects, and Patients With Premenstrual Syndrome *Murray B. Stein, Peter J. Schmidt, David R. Rubinow, and Thomas W. Uhde*

1304 Family History of Anxiety Disorders in Control Subjects With Lactate-Induced Panic Attacks *Richard Balon, Margaret Jordan, Robert Pohl, and Vikram K. Yeragani*

1307 A Longitudinal Assessment of Haloperidol Doses and Serum Concentrations in Asian and Caucasian Schizophrenic Patients *Keh-Ming Lin, Russell E. Poland, Inocencia Nuccio, Kazuko Matsuda, Nhuhy Hathuc, Tung-Ping Su, and Paul Fu*

1312 Diagnostic Legitimacy of Factitious Disorder With Psychological Symptoms *Richard Rogers, R. Michael Bagby, and Neil Rector*

1315 A Crosswalk From *DSM-III-R* to *ICD-9-CM* *James W. Thompson and Harold Pincus*

1320 Sex Differences in Olfactory Function in Schizophrenia *Lili Kopala, Campbell Clark, and Trevor A. Hurwitz*

COMMENTARY

1323 A Basic Residency Curriculum Concerning the Chronically Mentally Ill *Larry R. Faulkner, David L. Cutler, David D. Krohn, Robert M. Factor, Stephen M. Goldfinger, Charles R. Goldman, H. Richard Lamb, Harriet Lefley, Kenneth Minkoff, Stuart R. Schwartz, James H. Shore, and Allan Tasman*

CLINICAL AND RESEARCH REPORTS

1328 Obsessive-Compulsive Disorder: A Double-Blind, Placebo-Controlled Trial of Clomipramine in 27 Patients *Michael A. Jenike, Lee Baer, Paul Summergrad, Jeffrey B. Weilburg, Amy Holland, and Ralph Seymour*

1331 Benzodiazepine Use and Abuse by Patients at Outpatient Clinics *Arthur Rifkin, Seshagiri Doddi, Basawaraj Karajgi, Nusrath Hasan, and Luz Alvarez*

1333 Parental Alcoholism as a Risk Factor in Benzodiazepine Abuse: A Pilot Study *Domenic A. Ciraulo, Jamie G. Barnhill, Ann Marie Ciraulo, David J. Greenblatt, and Richard I. Shader*

BOOK FORUM 1336

LETTERS TO THE EDITOR 1349

OFFICIAL ACTIONS

Annual Reports to the Membership

1363 Report of the Secretary: Summary of Actions of the Board of Trustees, May 1988–May 1989
1372 Report of the Treasurer
1374 Report of the Medical Director
1379 Report of the Speaker
1382 Report of the Speaker-Elect
1384 Report of the Committee on Constitution and By-Laws
1384 Report of the Committee on Membership
1389 Report of the Committee of Tellers

1390 Guidelines Regarding Psychiatrists' Signatures

OTHER

A9 Officers of the American Psychiatric Association
A12 Calendar
A14 Books Received
A44 *British Journal of Psychiatry* Contents (August 1989)
A47 Information for Contributors
A51 *Psychological Medicine* Contents (August 1989)
A54 Index to Advertisers

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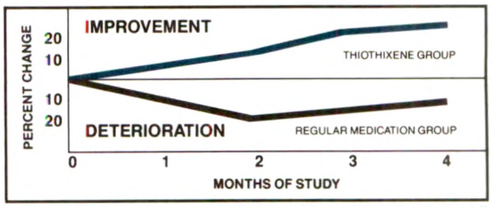

(Adapted from DiMascio and Demirgian[2,3])

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References: 1. Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. 2. DiMascio A, Demirgian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. 3. DiMascio A, Demirgian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association. Washington, DC, May 3-6, 1971. 4. Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients, in Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry.* Basel, Switzerland, S. Karger, 1969, vol 2, pp 45-52. 5. Dillenkoffer RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of the American Psychiatric Association, Dallas, May 1-4, 1972. 6. Data available on request from Roerig.

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Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythimas).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

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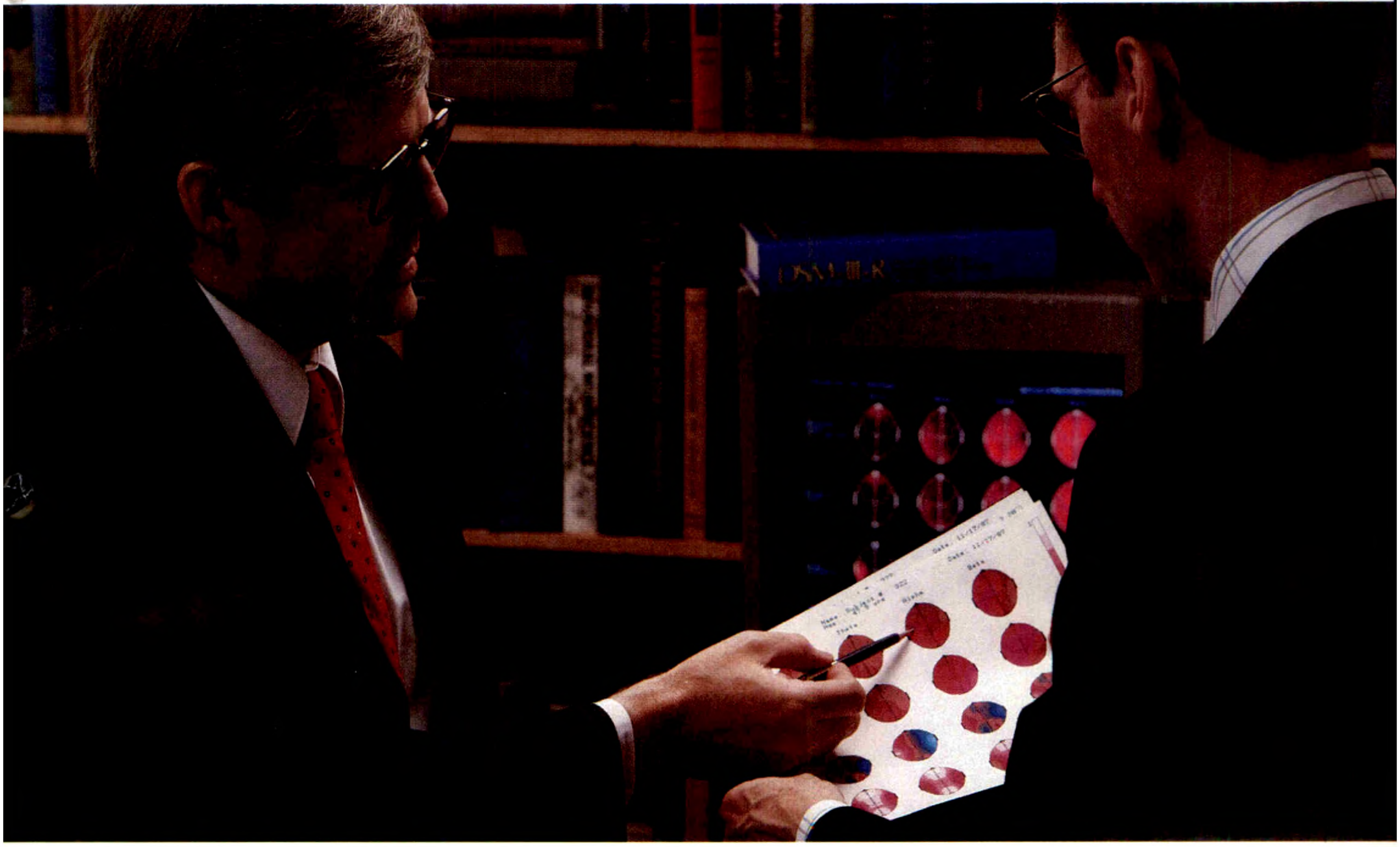

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DECEMBER

December 3–6, 6th Annual Northeast Regional Methadone Conference, Newport, Rhode Island. Contact Craig Stenning or Michael Rizzi, 908 Reservoir Avenue, Cranston, Rhode Island 02910; 401-461-5056.

December 5–7, 4th Pan Arab Congress on Psychiatry, Sana'a, Yemen Arab Republic. Contact Dr. Ahmed Mohamed Makki, Congress Secretary, P.O. Box 1390, Sana'a, Yemen Arab Republic; 203304 or 204487.

December 6–8, 9th World Congress of Sexology, Caracas, Venezuela. Contact Organizing Committee, 9th World Congress for Sexology, Apdo. Postal 17302, Caracas 1015A, Venezuela.

December 11–15, International Conference on General Hospital Psychiatry, Cerromar Beach, Puerto Rico. Contact E. Perez, M.D., c/o Joan Bradden, Department of Psychiatry, Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario, Canada K1Y 4E9; 613-725-4787.

JANUARY

January 21–27, 16th Annual Meeting of the Southern Clinical Neurological Society, Islamorado, Florida. Contact Millie F. Walden, Executive Secretary, 3425 S.W. 2nd Avenue, #153, Gainesville, FL 32607; 904-374-6058 or 904-373-9765.

FEBRUARY

February 5–9, 12th Annual British Virgin Islands Medical Conference, Road Town, Tortola. Contact Butterworth Hospital, 100 Michigan, Northeast, Grand Rapids, Michigan; 616-732-2666.

February 12–14, 3rd Annual Research Conference on "A System of Care for Children: Building the Research Base," Tampa, Florida. Contact Alissa Algarin, RTCCMH, Florida Mental Health Institute, 13301 Bruce B. Downs Blvd., Tampa, FL 33612-3899; 813-974-4500.

MARCH

March 28–April 1, 18th Annual Meeting of the American Society for Psychosomatic Obstetrics and Gynecology, New York. Contact Patricia D. Stahr, Administrator, Liaison Activities, The American College of Obstetricians and Gynecologists, 409 12th Street, SW, Washington, DC 20024-2188; 202-863-2514.

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References: 1. Thompson TL II, Thompson WL. Treating depression: tricyclics, tetracyclics, and other options. *Modern Medicine.* August 1983;51:87-109. **2.** Georgotas A. Affective disorders: pharmacotherapy. In: Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry IV.* Baltimore, Md: Williams & Wilkins; 1985;1:821-833. **3.** Bye C, Clubley M, Peck AW. Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol.* 1978;6:155-161. **4.** Kupfer DJ, Spiker DG, Rossi A, Coble PA, Shaw D, Ulrich R. Nortriptyline and EEG sleep in depressed patients. *Biol Psychiatry.* 1982;17:535-546. **5.** Blackwell B, Peterson GR, Kuzma RJ, Hostetler RM, Adolph AB. The effect of five tricyclic antidepressants on salivary flow and mood in healthy volunteers. *Communications in Psychopharmacol.* 1980;4:255-261. **6.** Hayes PE, Kristoff CA. Adverse reactions to five new antidepressants. *Clin Pharm.* 1986;5:471-480. **7.** Ziegler VE, Clayton PJ, Biggs JT. A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry.* May 1977;34:607-612.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor® (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

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The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher A.U.C. and lower clearance of nortriptyline.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia. *Withdrawal Symptoms*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage.

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Books Received

Freud on Instinct and Morality, by Donald C. Abel. Albany, State University of New York Press, 1989, 120 pp., $34.50; $10.95 (paper).

The Visible and Invisible Group: Two Perspectives on Group Psychotherapy and Group Process (1981), by Yvonne Agazarian and Richard Peters. New York, Tavistock/Routledge, 1989, 287 pp., $17.95 (paper).

Thinking in the Shadow of Feelings: A New Understanding of the Hidden Forces That Shape Individuals and Societies, by Reuven Bar-Levav, M.D. New York, Simon & Schuster, 1988, 351 pp., $10.95.

Beyond Codependency and Getting Better All the Time, by Melody Beattie. Center City, Minn., Hazelden, 1989, 252 pp., no price listed.

Who Killed Virginia Woolf? A Psychobiography, by Alma Halbert Bond, Ph.D. New York, Insight Books (Human Sciences Press), 1989, 194 pp., $19.95.

Defining Rape, by Linda Brookover Bourque. Durham, N.C., Duke University Press, 1989, 410 pp., $59.95.

Psychiatric Dictionary, 6th ed., by Robert Jean Campbell, M.D. New York, Oxford University Press, 1989, 811 pp., $45.00.

When Life Isn't Fair, by Dwight Carlson, M.D., and Susan Carlson Wood. Eugene, Ore., Harvest House, 1989, 229 pp., $6.95 (paper).

Swept Away: Why Women Confuse Love and Sex (1984), by Carol Cassell, Ph.D. New York, Fireside Books (Simon & Schuster), 1989, 208 pp., $8.95 (paper).

Armies in Low-Intensity Conflict: A Comparative Analysis, edited by David A. Charters and Maurice Tugwell. Oxford, Brassey's Defence Publishers (Pergamon Press), 1989, 256 pp., $39.95.

The Technique and Practice of Listening in Intensive Psychotherapy, by Richard D. Chessick, M.D., Ph.D. Northvale, N.J., Jason Aronson, 1989, 266 pp., $27.50.

The Ordinary Is Extraordinary: How Children Under Three Learn (1988), by Amy Laura Dombro and Leah Wallach. New York, Fireside Books (Simon & Schuster), 1989, 327 pp., $8.95 (paper).

The Broken Cord, by Michael Dorris. New York, Harper & Row, 1989, 300 pp., $18.95.

Four Therapeutic Approaches to the Borderline Patient: Principles and Techniques of the Basic Dynamic Stances, by Andrew B. Druck, Ph.D. Northvale, N.J., Jason Aronson, 1989, 412 pp., $40.00.

Human Ethology, by Irenäus Eibl-Eibesfeldt. New York, Aldine de Gruyter, 1989, 804 pp., $69.95.

Psychological Defenses in Everyday Life, by Robert W. Firestone, Ph.D., and Joyce Catlett, M.A. New York, Insight Books (Human Sciences Press), 1989, 256 pp., $16.95 (paper).

Intimate Violence (1988), by Richard J. Gelles, Ph.D., and Murray A. Straus, Ph.D. New York, Touchstone Books (Simon & Schuster), 1989, 288 pp., $10.95 (paper).

Children of Color: Psychological Interventions With Minority Youth, by Jewelle Taylor Gibbs and Larke Nahme Huang and associates. San Francisco, Jossey-Bass, 1989, 403 pp., $27.95.

Molecular and Cellular Aspects of the Drug Addictions, edited by Avram Goldstein, M.D. New York, Springer Verlag, 1989, 222 pp., $59.00.

Raising a Child Conservatively in a Sexually Permissive World, revised ed., by Sol Gordon, Ph.D., and Judith Gordon, M.S.W. New York, Fireside Books (Simon & Schuster), 1989, 234 pp., $8.95 (paper).

Group Psychodynamics: New Paradigms and New Perspectives, edited by David A. Halperin, M.D. Chicago, Year Book Medical Publishers, 1989, 325 pp., no price listed.

Clinical Case Management: New Directions for Mental Health Services, number 40, winter 1988, edited by Maxine Harris and Leona L. Bachrach; H. Richard Lamb, editor-in-chief. San Francisco, Jossey-Bass, 1988, 96 pp., $14.95 (paper).

Nuances of Technique in Dynamic Psychotherapy, by Mardi J. Horowitz, M.D. Northvale, N.J., Jason Aronson, 1989, 268 pp., $27.50.

Philosophy, Psychiatry, and Neuroscience: Three Approaches to the Mind. A Synthetic Analysis of the Varieties of Human Experience, by Edward M. Hundert. New York, Clarendon Press (Oxford University Press), 1989, 338 pp., $39.95.

Self-Renewal: A Workbook for Achieving High Performance and Health in a High-Stress Environment (1984), by Dennis T. Jaffe, Ph.D., and Cynthia D. Scott, Ph.D., M.P.H. New York, Fireside Books (Simon & Schuster), 1989, 193 pp., $10.95 (paper).

Geriatric Psychiatry and Psychopharmacology: A Clinical Approach, by Michael A. Jenike, M.D. Chicago, Year Book Medical Publishers, 1989, 381 pp., no price listed.

Hazards of Psychiatric Practice: A Clinical and Legal Guide for the Therapist, by Peter L. Jenkins, M.B., B.S., B.Sc., M.R.C.Psych. Chicago, Year Book Medical Publishers, 1989, 161 pp., no price listed (paper).

Comprehensive Textbook of Psychiatry, 5th ed., vols. 1 and 2, edited by Harold I. Kaplan, M.D., and Benjamin J. Sadock, M.D. Baltimore, Williams & Wilkins, 1989, 2,158 pp., no price listed.

Handbook of Psychiatry and the Law, by Ebrahim J. Kermani, M.D. Chicago, Year Book Medical Publishers, 1989, 292 pp., no price listed (paper).

Handbook of Clinical Assessment of Children and Adolescents, vols. I, II, edited by Clarice J. Kestenbaum and Daniel T. Williams. New York, New York University Press (Columbia University Press, distributor), 1988, 1,146 pp., $75.00.

Treatment of Victims of Sexual Abuse: The Psychiatric Clinics of North America, vol. 12, number 2, June 1989, edited by Richard P. Kluft, M.D. Philadelphia, W.B. Saunders Co. (Harcourt Brace Jovanovich), 1989, 264 pp., no price listed.

The Imperfect Therapist: Learning From Failure in Therapeutic Practice, by Jeffrey A. Kottler and Diane S. Blau. San Francisco, Jossey-Bass, 1989, 181 pp., $19.95.

The Art of Unknowing: Dimensions of Openness in Analytic Therapy, by Stephen Kurtz, C.S.W. Northvale, N.J., Jason Aronson, 1989, 255, $25.00.

Modern Madness: The Hidden Link Between Work and Emotional Conflict (1986), by Douglas LaBier. New York, Touchstone (Simon & Schuster), 1989, 244 pp., $10.95 (paper).

Opportunistic Infections in Patients With the Acquired Immunodeficiency Syndrome, edited by Gifford Leoung and John Mills. New York, Marcel Dekker, 1989, 434 pp., $89.75.

New Directions in Affective Disorders, edited by Bernard Lerer and Samuel Gershon. New York, Springer Verlag, 1989, 709 pp., $150.00.

Night and Day, by Jack Maguire. New York, Roundtable Press, Fireside Books (Simon & Schuster), 1989, 221 pp., $8.95 (paper).

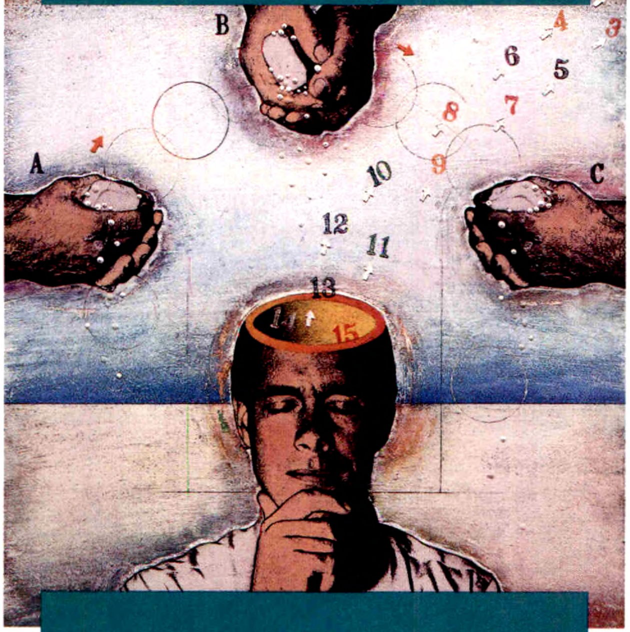
Painful Choices: Research and Essays on Health Care, by David Mechanic. New Brunswick, N.J., Transaction Publishers, 1989, 248 pp., $34.95.

Treating Schizophrenia, by Werner M. Mendel. San Francisco, Jossey-Bass, 1989, 233 pp., $24.95.

Legal Implications of Hospital Policies and Practices: New Directions for Mental Health Services, number 41, spring 1989, edited by Robert D. Miller; H. Richard Lamb, editor-in-chief. San Francisco, Jossey-Bass, 1989, 118 pp., $14.95 (paper).

(Continued on page A16)

CIBA-GEIGY ANNOUNCES



A treatment IND (investigational new drug) program for patients with Obsessive-Compulsive Disorder

FDA procedures now bring promising investigational drugs to patients earlier in the development process.

The Food and Drug Administration has established procedures to allow use of "...promising drugs for treatment of patients with serious or life-threatening illnesses..."[1] as early in the drug development process as possible and before general marketing has begun.

This OCD medication is the first psychotropic drug authorized under these new procedures.

In releasing the drug for treatment use, the FDA explained that "...studies aimed at U.S. approval... have shown sufficient evidence of effectiveness for the drug to permit its limited distribution."[2]

For information and enrollment kits call

1-800-842-2422

between 9AM-5PM Eastern Time

Ready supply of drug available through enrolled psychiatrists for eligible patients.

The treatment medication is being distributed by CIBA-GEIGY free of charge to psychiatrists enrolled in the treatment IND program, who will, in turn, supply the drug to eligible patients.

Patient enrollment criteria established.

Patients must be between 10 and 70 years of age, with OCD symptoms of at least one year's duration that interfere significantly with daily functioning.

---

[1] Young FE, Benson JS, Nightingale SL, et al: Drugs available under treatment IND. *FDA Drug Bulletin* 1988:18:14-15.

[2] FDA Press Release, June 6, 1988.

Announced by
CIBA–GEIGY
Pharmaceuticals
Summit, New Jersey 07901

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Books Received

(Continued from page A14)

Familial Alzheimer's Disease: Molecular Genetics and Clinical Perspectives, edited by Gary D. Miner, Ralph W. Richter, John P. Blass, Jimmie L. Valentine, and Linda A. Winters-Miner. New York, Marcel Dekker, 1989, 408 pp., $125.00.

Computer-Intensive Methods for Testing Hypotheses: An Introduction, by Eric W. Noreen. New York, Wiley-Interscience (John Wiley & Sons), 1989, 226 pp., $24.95 (paper).

Handbook of Symptom-Oriented Neurology, by William H. Olson, M.D., Roger A. Brumback, M.D., Generoso Gascon, M.D., and Vasudeva Iyer, M.D. Chicago, Year Book Medical Publishers, 1989, 376 pp., no price listed (paper).

Women's Disorders: The Psychiatric Clinics of North America, vol. 12, number 1, March 1989, edited by Barbara L. Parry, M.D. Philadelphia, W.B. Saunders Co. (Harcourt Brace Jovanovich), 1989, 230 pp., no price listed.

Dreams of Love and Fateful Encounters: The Power of Romantic Passion (1988), by Ethel S. Person. New York, Penguin Books, 1989, 376 pp., $8.95 (paper).

Disturbing the Nest: Family Change and Decline in Modern Societies, by David Popenoe. New York, Aldine de Gruyter, 1988, 375 pp., $49.95; $24.95 (paper).

Flowing Bridges, Quiet Waters: Japanese Psychotherapies, Morita and Naikan, by David K. Reynolds. Albany, State University of New York Press, 1989, 187 pp., $34.50; $10.95 (paper).

Aging and Clinical Practice: Depression and Coexisting Disease, edited by Robert G. Robinson, M.D., and Peter V. Rabins, M.D. New York, Igaku-Shoin, 1989, 233 pp., $29.95 (paper).

Empathic Attunement: The "Technique" of Psychoanalytic Self Psychology, by Crayton E. Rowe, Jr., M.S.W., and David S. Mac Isaac, Ph.D. Northvale, N.J., Jason Aronson, 1989, 310 pp., $30.00.

Merritt's Textbook of Neurology, 8th ed., edited by Lewis P. Rowland, M.D. Philadelphia, Lea & Febiger, 1989, 928 pp., $67.50.

Practical Concerns About Siblings: Bridging the Research-Practice Gap. Journal of Children in Contemporary Society, vol. 19, numbers 3/4, spring/summer 1987, edited by Frances Fuchs Schacter, Ph.D., and Richard K. Stone, M.D. New York, Haworth Press, 1987, 205 pp., $34.95.

Schizophrenia: Scientific Progress, edited by S. Charles Schulz, M.D., and Carol A. Tamminga, M.D. New York, Oxford University Press, 1989, 410 pp., $65.00.

Social Order/Mental Disorder: Anglo-American Psychiatry in Historical Perspective, by Andrew Scull. Berkeley, University of California Press, 1989, 350 pp., $25.00.

The Triarchic Mind: A New Theory of Human Intelligence (1988), by Robert J. Sternberg. New York, Penguin Books, 1989, 346 pp., $8.95 (paper).

Surgeon General's Workshop on Drunk Driving: Proceedings. Rockville, Md., U.S. Department of Health and Human Services, Public Health Service, 1989, 106 pp., no price listed (paper).

The Biopsychology of Mood and Arousal, by Robert E. Thayer. New York, Oxford University Press, 1989, 222 pp., $35.00.

Secret Scars: A Guide for Survivors of Child Sexual Abuse (1988), by Cynthia Crosson Tower. New York, Penguin Books, 1989, 201 pp., $7.95 (paper).

Kids and Guns: A Child Safety Scandal, 2nd ed., by William W. Treanor and Marjolijn Bijlefeld. Washington, D.C., American Youth Work Center and the Educational Fund to End Handgun Violence, 1989, 41 pp., no price listed (paper).

Willpower's Not Enough: Understanding and Recovering From Addictions of Every Kind, by Arnold M. Washton, Ph.D., and Donna Boundy, M.S.W. New York, Harper & Row, 1989, 272 pp., $18.95.

Lexicon of Psychiatric and Mental Health Terms, vol. 1, by the World Health Organization. Geneva, WHO, 1989, 67 pp., no price listed (paper).

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENTS

Feeling better
Living better

NEW **Wellbutrin**®
(BUPROPION HCl)

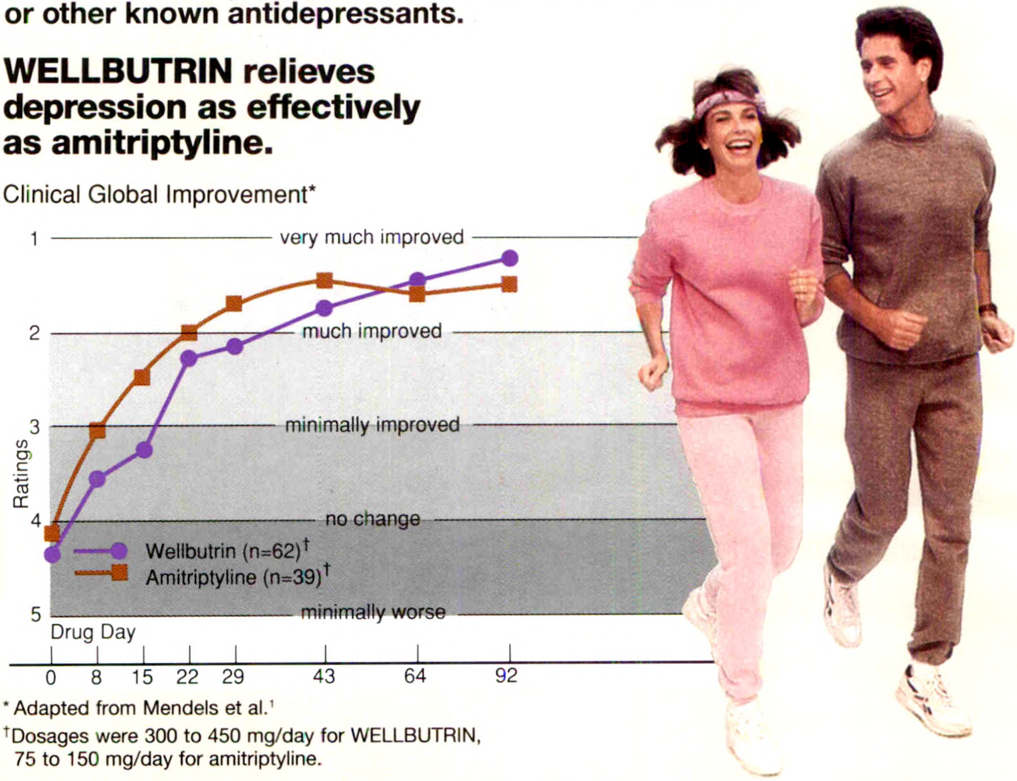
helps clear depression with few life-style disruptions.

See brief summary of full prescribing information on last pages of this advertisement.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENTS

Chemically unique WELLBUTRIN is unrelated to tricyclics/tetracyclics, monoamine oxidase inhibitors, or other known antidepressants.

WELLBUTRIN relieves depression as effectively as amitriptyline.



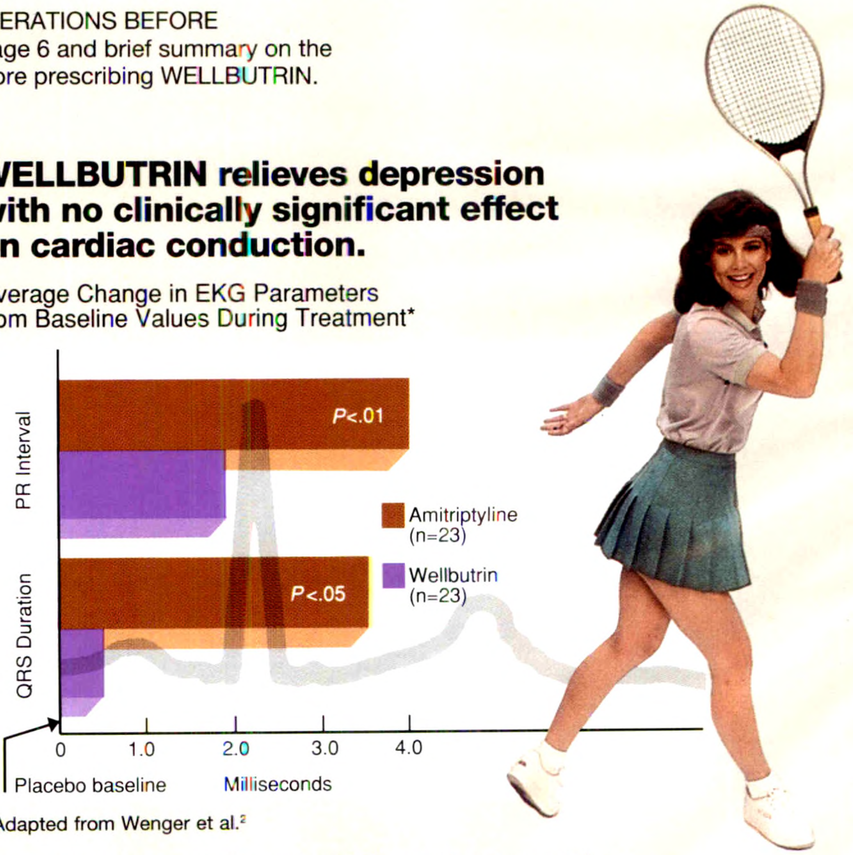
Clinical Global Improvement*

* Adapted from Mendels et al.[1]

†Dosages were 300 to 450 mg/day for WELLBUTRIN, 75 to 150 mg/day for amitriptyline.

Please review IMPORTANT CONSIDERATIONS BEFORE PRESCRIBING WELLBUTRIN on page 6 and brief summary on the last pages of this advertisement before prescribing WELLBUTRIN.

WELLBUTRIN relieves depression with no clinically significant effect on cardiac conduction.



Average Change in EKG Parameters from Baseline Values During Treatment*

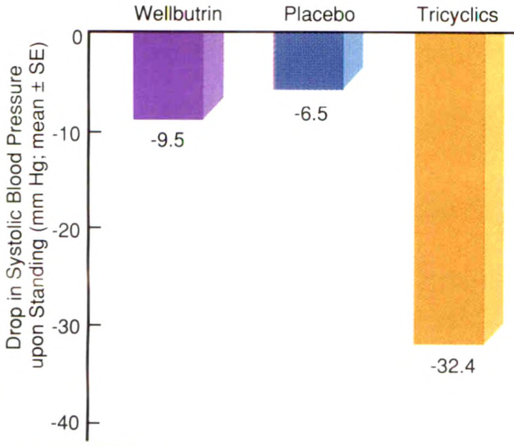
* Adapted from Wenger et al.[2]

"By contrast, the present results with bupropion support the in vitro data demonstrating that this antidepressant lacks these undesirable electro-physiologic properties, and imply that bupropion has a substantially wider margin of safety in man than amitriptyline with regard to cardiac conduction."[2]

Feeling better
Living better

WELLBUTRIN relieves depression with no clinically significant orthostatic hypotension.

Orthostatic Blood Pressure Change (mm Hg)*



* Adapted from Farid et al.[3]

NEW **Wellbutrin**®

(BUPROPION HCl)

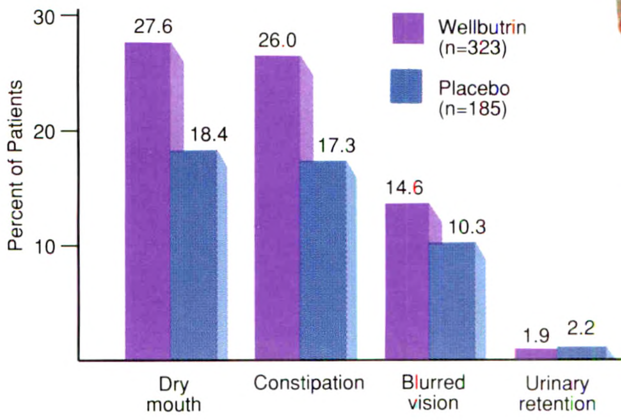
Helping patients to feel better and live better.

See brief summary of full prescribing information on last pages of this advertisement.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENTS

WELLBUTRIN relieves depression with few anticholinergic side effects.

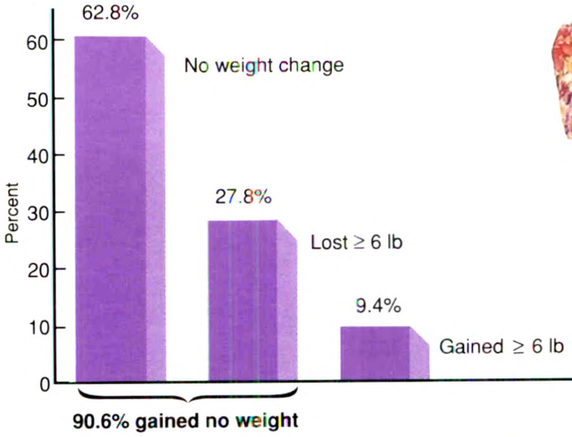
Percent Difference in Anticholinergic Effects Relative to Placebo*



* Data on file, Burroughs Wellcome Co.[4]

WELLBUTRIN relieves depression with little or no weight gain.

Change in Body Weight (percent of patients; n=341)*

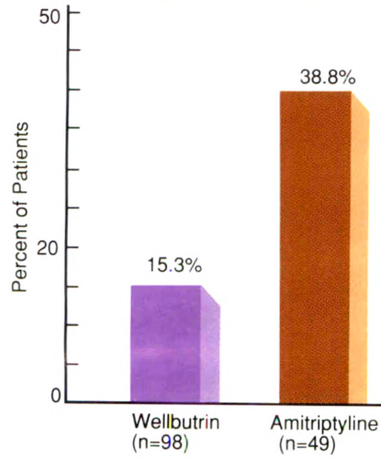


* Data on file, Burroughs Wellcome Co.[4]

Feeling better
Living better

WELLBUTRIN relieves depression with little or no daytime drowsiness.

Percent of Patients Reporting Treatment-Related Drowsiness*



* Data on file, Burroughs Wellcome Co.[4]

In placebo-controlled clinical trials, the incidence of drowsiness* for patients treated with WELLBUTRIN was 19.8%, versus 19.5% for those receiving placebo.

Agitation and Insomnia: A substantial proportion of patients treated with WELLBUTRIN experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of WELLBUTRIN treatment.

**As with all drugs in this category, patients should be cautioned that the ability to perform tasks requiring judgment or motor and cognitive skills may be impaired.*

P_24 371

NEW Wellbutrin®

(BUPROPION HCl)

Helping patients to feel better and live better.

See brief summary of full prescribing information on last pages of this advertisement.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENTS

Feeling better
Living better

Wellbutrin® (bupropion HCl) helps clear depression with few life-style disruptions.

Important considerations before prescribing Wellbutrin.

Patient Selection Criteria
WELLBUTRIN is contraindicated in patients

- with a seizure disorder
- with a current or prior diagnosis of bulimia or anorexia nervosa
- on monoamine oxidase (MAO) inhibitor therapy
- who are allergic to it

(See CONTRAINDICATIONS section of full prescribing information.)

WELLBUTRIN should be administered with extreme caution to patients

- with a history of seizure, cranial trauma, or other factors that predispose toward seizure
- taking other agents or other treatment regimens that may lower seizure threshold

(See WARNINGS section of full prescribing information.)

Overdosage
In 13 cases of overdose involving WELLBUTRIN, there were no deaths or lasting sequelae.

Seizures
A wide range of seizure rates have been reported with antidepressant therapy with some reports as low as 0.1%. The incidence of seizures with WELLBUTRIN is approximately 0.4%, which may be as much as fourfold higher than some other antidepressants, although no direct comparative studies have been conducted.

Dosage and Administration
The recommended starting dose of WELLBUTRIN is 200 mg/day given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day given as 100 mg t.i.d. no sooner than three days after beginning therapy.

Dosing Regimen

Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets		
			Morning	Midday	Evening
1-3	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Increases in dose should not exceed 100 mg/day in a three-day period. WELLBUTRIN is available in both 75 mg and 100 mg tablets.

Important: No single dose of WELLBUTRIN should exceed 150 mg because a higher incidence of seizures has been observed in patients receiving higher individual doses of WELLBUTRIN. For this reason, too, patients should be reminded that they should not double up on any dose because they missed a previous one. Dosage should not exceed 450 mg per day (see WARNINGS).

Clinical trials involving more than 7,000 depressed patients and over 200 investigators demonstrated that **WELLBUTRIN relieves depression in a wide range of patients:**

- with no clinically significant effects on cardiac conduction
- with no clinically significant orthostatic hypotension
- with few anticholinergic side effects
- with little or no weight gain
- with little or no daytime drowsiness

NEW Wellbutrin
(BUPROPION HCl)

See brief summary of full prescribing information on last pages of this advertisement.

WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Wellbutrin is indicated for the treatment of depression. A physician considering the initiation of Wellbutrin should be aware that the drug may cause generalized seizures with an approximate incidence of 0.4% (4/1000). This incidence may exceed that of other antidepressants as much as fourfold. This relative risk is only an approximation since no direct comparative studies have been conducted.

CONTRAINDICATIONS: Wellbutrin is contraindicated in patients: with a seizure disorder; with a current or prior diagnosis of bulimia or anorexia nervosa, because of a higher incidence of seizures noted in such patients; who have shown an allergic response to it; or who are currently being treated with an MAO inhibitor. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Wellbutrin.

WARNINGS:

SEIZURES: Wellbutrin is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for Wellbutrin increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third the maximum recommended daily dose (450 mg). Given the wide variability among individuals and their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

During the pre-approval evaluation period, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, 7 patients were receiving daily doses of 450 mg or below, for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve (12) patients experienced seizures at 600 mg per day (2.3% incidence); 6 additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

A separate, prospective study was conducted to determine the incidence of seizure during an 8 week treatment exposure in approximately 3200 additional patients who received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond 8 weeks if clinically indicated. Eight (8) seizures occurred during the initial 8 week treatment period and 5 seizures were reported in patients continuing treatment beyond 8 weeks, resulting in a total seizure incidence of 0.4%.

The risk of seizure appears to be strongly associated with dose and the presence of predisposing factors. A significant predisposing factor (e.g., history of head trauma or prior seizure, CNS tumor, concomitant medications that lower seizure threshold, etc.) was present in approximately one-half of the patients experiencing a seizure. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose.

***Recommendations for reducing the risk of seizure:* Retrospective analysis of clinical experience gained during the development of Wellbutrin suggests that the risk of seizure may be minimized if (1) the total daily dose of Wellbutrin does *not* exceed 450 mg, (2) the daily dose is administered t.i.d., with each single dose *not* to exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites, and (3) the rate of incrementation of dose is very gradual. Extreme caution should be used when Wellbutrin is (1) administered to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or (2) prescribed with other agents (e.g., antipsychotics, other antidepressants, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.**

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatotoxin in humans.

PRECAUTIONS:

General:

Agitation and Insomnia: A substantial proportion of patients treated with Wellbutrin experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of Wellbutrin treatment.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Patients treated with Wellbutrin have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Wellbutrin. In several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in Bipolar Manic Depressive patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin is expected to pose similar risks.

Altered Appetite and Weight: A weight loss of greater than 5 pounds occurred in 28% of Wellbutrin patients. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 34.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with Wellbutrin did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of Wellbutrin should be considered.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for Wellbutrin should be written for the smallest number of tablets consistent with good patient management.

Use in Patients with Systemic Illness: There is no clinical experience establishing the safety of Wellbutrin in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Wellbutrin was well tolerated in patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants.

Because bupropion HCl and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients beyond concentrations expected in patients without renal or hepatic impairment. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

Information for Patients:

Patients should be instructed to take Wellbutrin in equally divided doses three or four times a day to minimize the risk of seizure.

Patients should be told that any CNS-active drug like Wellbutrin may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that Wellbutrin does not adversely affect their performance they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the use and cessation of use of alcohol may alter the seizure threshold, and, therefore, that the consumption of alcohol should be minimized, and, if possible, avoided completely.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Drug Interactions: No systematic data have been collected on the consequences of the concomitant administration of Wellbutrin and other drugs.

However, animal data suggest that Wellbutrin may be an inducer of drug metabolizing enzymes. This may be of potential clinical importance because the blood levels of co-administered drugs may be altered.

Alternatively, because bupropion is extensively metabolized, the co-administration of other drugs may affect its clinical activity. In particular, care should be exercised when administering drugs known to affect hepatic drug metabolizing enzyme systems (e.g., carbamazepine, cimetidine, phenobarbital, phenytoin).

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of Wellbutrin and L-dopa. Administration of Wellbutrin to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small gradual dose increases.

Concurrent administration of Wellbutrin and agents which lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and small gradual dose increases should be employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a borderline positive response (2-3 times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance of these results in estimating the risk of human exposure to therapeutic doses is unknown.

A fertility study was performed in rats; no evidence of impairment of fertility was encountered at oral doses up to 300 mg/kg/day.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B: Reproduction studies have been performed in rabbits and rats at doses up to 15-45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in two studies, but there was no increase in any specific abnormality). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: The effect of Wellbutrin on labor and delivery in humans is unknown.

Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from Wellbutrin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of Wellbutrin in individuals under 18 years old have not been established.

Use in the Elderly: Wellbutrin has not been systematically evaluated in older patients.

ADVERSE REACTIONS: (See also WARNINGS and PRECAUTIONS) Adverse events commonly encountered in patients treated with Wellbutrin are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

Adverse events were sufficiently troublesome to cause discontinuation of Wellbutrin treatment in approximately ten percent of the 2400 patients and volunteers who participated in the product's pre-approval clinical trials. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENTS

The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Wellbutrin under relatively similar conditions of daily dosage (300-600 mg), setting, and duration (3-4 weeks). The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of Wellbutrin is provided in the WARNINGS and PRECAUTIONS sections.

TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS*
(Percent of Patients Reporting)

Adverse Experience	**Wellbutrin Patients (n = 323)**	**Placebo Patients (n = 185)**
CARDIOVASCULAR		
Cardiac Arrhythmias	5.3	4.3
Dizziness	22.3	16.2
Hypertension	4.3	1.6
Hypotension	2.5	2.2
Palpitations	3.7	2.2
Syncope	1.2	0.5
Tachycardia	10.8	8.6
DERMATOLOGIC		
Pruritus	2.2	0.0
Rash	8.0	6.5
GASTROINTESTINAL		
Anorexia	18.3	18.4
Appetite Increase	3.7	2.2
Constipation	26.0	17.3
Diarrhea	6.8	8.6
Dyspepsia	3.1	2.2
Nausea/Vomiting	22.9	18.9
Weight Gain	13.6	22.7
Weight Loss	23.2	23.2
GENITOURINARY		
Impotence	3.4	3.1
Menstrual Complaints	4.7	1.1
Urinary Frequency	2.5	2.2
Urinary Retention	1.9	2.2
MUSCULOSKELETAL		
Arthritis	3.1	2.7
NEUROLOGICAL		
Akathisia	1.5	1.1
Akinesia/Bradykinesia	8.0	8.6
Cutaneous Temperature Disturbance	1.9	1.6
Dry Mouth	27.6	18.4
Excessive Sweating	22.3	14.6
Headache/Migraine	25.7	22.2
Impaired Sleep Quality	4.0	1.6
Increased Salivary Flow	3.4	3.8
Insomnia	18.6	15.7
Muscle Spasms	1.9	3.2
Pseudoparkinsonism	1.5	1.6
Sedation	19.8	19.5
Sensory Disturbance	4.0	3.2
Tremor	21.1	7.6
NEUROPSYCHIATRIC		
Agitation	31.9	22.2
Anxiety	3.1	1.1
Confusion	8.4	4.9
Decreased Libido	3.1	1.6
Delusions	1.2	1.1
Disturbed Concentration	3.1	3.8
Euphoria	1.2	0.5
Hostility	5.6	3.8
NONSPECIFIC		
Fatigue	5.0	8.6
Fever/Chills	1.2	0.5
RESPIRATORY		
Upper Respiratory Complaints	5.0	11.4
SPECIAL SENSES		
Auditory Disturbance	5.3	3.2
Blurred Vision	14.6	10.3
Gustatory Disturbance	3.1	1.1

*Events reported by at least 1% of Wellbutrin patients are included.

Other events observed during the entire pre-approval evaluation of Wellbutrin: During its pre-approval assessment, Wellbutrin was evaluated in almost 2400 subjects. The conditions and duration of exposure to Wellbutrin varied greatly and a substantial proportion of the experience was gained in open and uncontrolled clinical settings. During this experience, numerous adverse events were reported; however, without appropriate controls, it is impossible to determine with certainty which events were or were not caused by Wellbutrin. The following enumeration is organized by organ system and describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections of the labeling.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular: Frequent was edema; infrequent were chest pain, EKG abnormalities (premature beats and nonspecific ST-T changes), and shortness of breath/dyspnea; and rare were pallor and phlebitis.

Dermatologic: Frequent were nonspecific rashes; infrequent were alopecia and dry skin; rare were change in hair color and hirsutism.

Endocrine: Infrequent was gynecomastia; rare were glycosuria and hormone level change.

Gastrointestinal: Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice; rare were rectal complaints, colitis, G.I. bleeding, and intestinal perforation.

Genitourinary: Frequent was nocturia; infrequent were vaginal irritation, testicular swelling, urinary tract infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia, and painful ejaculation.

Hematologic/Oncologic: Rare was lymphadenopathy.

Neurological: (see WARNINGS) Frequent were ataxia/incoordination, seizure, myoclonus, dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; and rare were EEG abnormality, abnormal neurological exam, impaired attention, and sciatica.

Neuropsychiatric: (see PRECAUTIONS) Frequent were mania/hypomania, increased libido, hallucinations, decrease in sexual function, and depression; infrequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder, and frigidity; rare was suicidal ideation.

Oral Complaints: Frequent was stomatitis; infrequent were toothache, bruxism, gum irritation, and oral edema; rare was glossitis.

Respiratory: Infrequent were bronchitis and shortness of breath/dyspnea; rare were epistaxis and rate or rhythm disorder.

Special Senses: Infrequent was visual disturbance; rare was diplopia.

Nonspecific: Frequent were flu-like symptoms; infrequent was nonspecific pain; rare were body odor, surgically related pain, infection, medication reaction and overdose.

Post-Approval Reports: The following additional events were rarely observed (less than 1/1000 patients) post-approval.

Cardiovascular: Flushing and myocardial infarction.

Dermatologic: Acne.

Gastrointestinal: Stomach ulcer.

Hematologic/Oncologic: Anemia and pancytopenia.

Neurological: Aphasia.

Musculoskeletal: Musculoskeletal chest pain.

Respiratory: Pneumonia and pulmonary embolism.

OVERDOSAGE:

Human overdose experience: There has been limited clinical experience with overdosage of Wellbutrin. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of Wellbutrin and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

DOSAGE AND ADMINISTRATION:

General Dosing Considerations: It is particularly important to administer Wellbutrin in a manner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose should not exceed 100 mg/day in a 3 day period. Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped.

No single dose of Wellbutrin should exceed 150 mg. Wellbutrin should be administered t.i.d., preferably with at least 6 hours between successive doses.

Usual Dosage for Adults: The usual adult dose is 300 mg/day, given t.i.d. Dosing should begin at 200 mg/day, given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day given as 100 mg t.i.d., no sooner than 3 days after beginning therapy (see table below).

Dosing Regimen

Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets		
			Morning	Midday	Evening
1	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

Increasing the Dosage Above 300 mg/Day: As with other antidepressants, the full antidepressant effect of Wellbutrin may not be evident until 4 weeks of treatment or longer. An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished using the 75 or 100 mg tablets. The 100 mg tablet must be administered q.i.d. with at least 4 hours between successive doses, in order not to exceed the limit of 150 mg in a single dose. Wellbutrin should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day.

Elderly Patients: In general, older patients are known to metabolize drugs more slowly and to be more sensitive to the anticholinergic, sedative, and cardiovascular side effects of antidepressant drugs.

References: **1.** Mendels J, Amin MM, Chouinard G, et al. A comparative study of bupropion and amitriptyline in depressed outpatients. *J Clin Psychiatry.* 1983;44(5, sec 2):118-120. **2.** Wenger TL, Cohn JB, Bustrack J. Comparison of the effects of bupropion and amitriptyline on cardiac conduction in depressed patients. *J Clin Psychiatry.* 1983;44(5, sec 2):174-175. **3.** Farid FF, Wenger TL, Tsai SY, et al. Use of bupropion in patients who exhibit orthostatic hypotension on tricyclic antidepressants. *J Clin Psychiatry.* 1983;44(5, sec 2):170-173. **4.** Data on file, Burroughs Wellcome Co.

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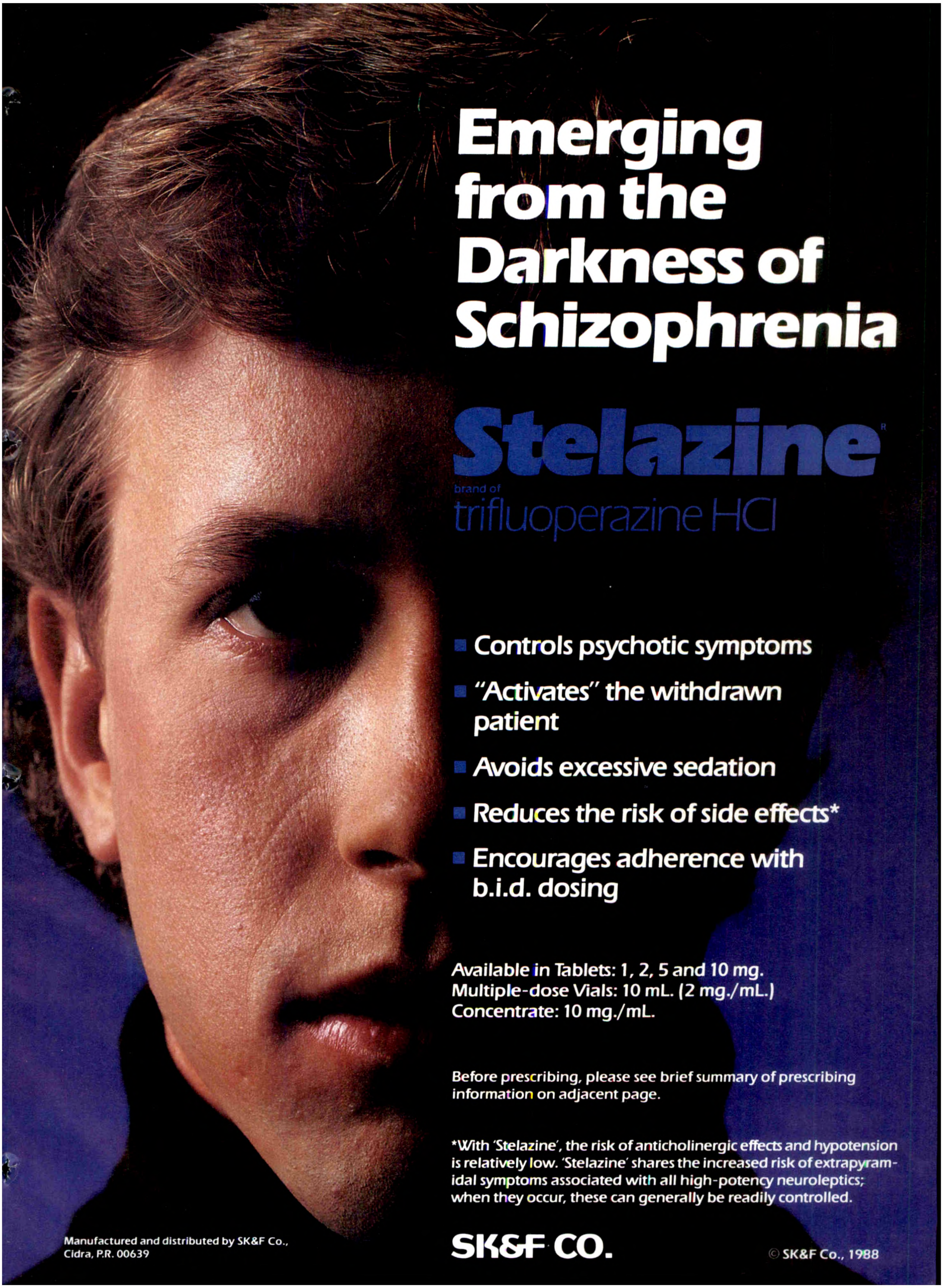

Emerging from the Darkness of Schizophrenia

Stelazine®

brand of

trifluoperazine HCl

- Controls psychotic symptoms
- "Activates" the withdrawn patient
- Avoids excessive sedation
- Reduces the risk of side effects*
- Encourages adherence with b.i.d. dosing

Available in Tablets: 1, 2, 5 and 10 mg.
Multiple-dose Vials: 10 mL. (2 mg./mL.)
Concentrate: 10 mg./mL.

Before prescribing, please see brief summary of prescribing information on adjacent page.

*With 'Stelazine', the risk of anticholinergic effects and hypotension is relatively low. 'Stelazine' shares the increased risk of extrapyramidal symptoms associated with all high-potency neuroleptics; when they occur, these can generally be readily controlled.

Manufactured and distributed by SK&F Co.,
Cidra, P.R. 00639

SK&F CO.

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Stelazine® brand of trifluoperazine HCl

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. The following is a brief summary.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations include: Hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment, if available, of any concomitant serious medical problems.

'Stelazine' Concentrate contains sodium bisulfite, which may cause allergic-type reactions including anaphylactic symptoms or asthmatic episodes in certain susceptible people. The prevalence of sulfite sensitivity in the general population is unknown and probably low and is seen more frequently in asthmatic than in non-asthmatic people.

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent in vitro, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecomastia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

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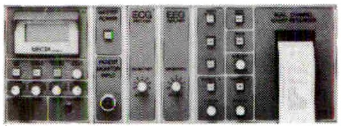

JR-1

FLEXIBILITY

SR/JR FEATURES INCLUDE:

- Continuous reading of energy in Joules
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- Bi-polar brief pulse stimulus
- Adjustable constant current stimulus
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- Remote control capabilities
- 100% expected seizure induction
- Totally isolated for maximum safety
- Single or multiple energy control(s)
- All parameters displayed in text form
- Increased energy for difficult cases
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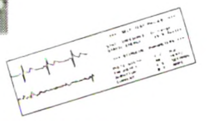
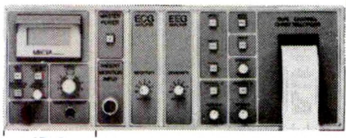
- Operates on 120 or 240 VAC
- Complete with all accessories



PRINTED SELF TEST AND TREATMENT RESULTS

SR-2



JR-2

ADDITIONAL FEATURES INCLUDED WITH ALL SR MODELS ARE:

- EEG instrumentation amplifier
- Built-in 2 channel digital chart recorder
- Numeric timing marks during monitoring
- Printed record of energy level
- Printed date and time of treatment
- ECG instrumentation amplifier
- Selectable single or dual channel
- Printed record of treatment and self test
- Printed record of stimulus parameters
- Modular design for maximum flexibility

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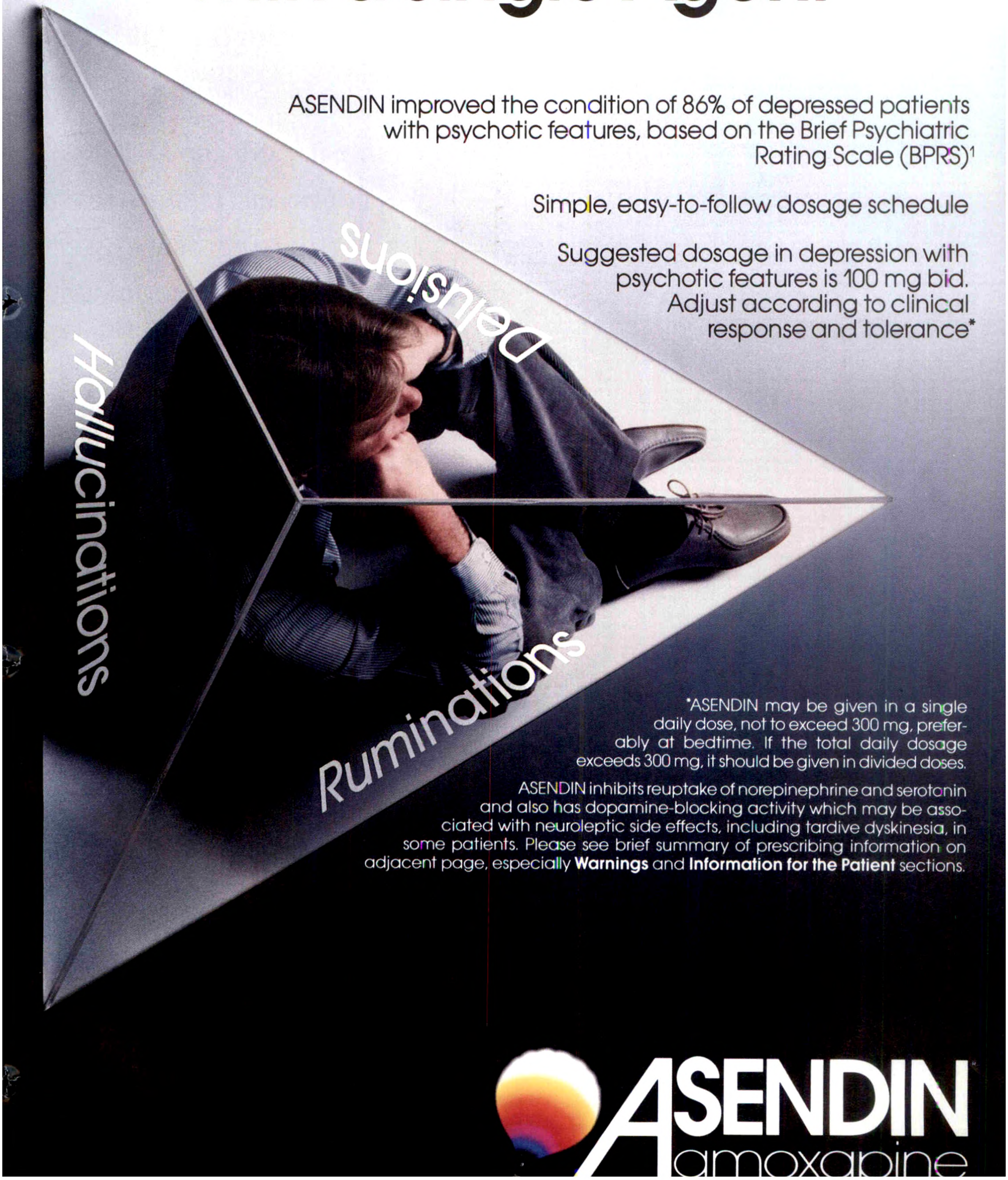
When Psychotic Features Complicate Depression

Simplify Therapy With a Single Agent



ASENDIN improved the condition of 86% of depressed patients with psychotic features, based on the Brief Psychiatric Rating Scale (BPRS)[1]

Simple, easy-to-follow dosage schedule

Suggested dosage in depression with psychotic features is 100 mg bid. Adjust according to clinical response and tolerance*

*ASENDIN may be given in a single daily dose, not to exceed 300 mg, preferably at bedtime. If the total daily dosage exceeds 300 mg, it should be given in divided doses.

ASENDIN inhibits reuptake of norepinephrine and serotonin and also has dopamine-blocking activity which may be associated with neuroleptic side effects, including tardive dyskinesia, in some patients. Please see brief summary of prescribing information on adjacent page, especially **Warnings** and **Information for the Patient** sections.

ASENDIN
amoxapine

ASENDIN® amoxapine Tablets
25 mg, 50 mg, 100 mg, 150 mg

CLINICAL PHARMACOLOGY

ASENDIN is an antidepressant with a mild sedative component to its action. The mechanism of its clinical action in man is not well understood. In animals, amoxapine reduced the uptake of norepinephrine and serotonin and blocked the response of dopamine receptors to dopamine. Amoxapine is not a monoamine oxidase inhibitor.

ASENDIN is absorbed rapidly and reaches peak blood levels approximately 90 minutes after ingestion. It is almost completely metabolized. The main route of excretion is the kidney. *In vitro* tests show that amoxapine binding to human serum is approximately 90%. In man, amoxapine serum concentration declines with a half-life of eight hours. However, the major metabolite, 8-hydroxyamoxapine, has a biologic half-life of 30 hours. Metabolites are excreted in the urine in conjugated form as glucuronides.

Clinical studies have demonstrated that ASENDIN has a more rapid onset of action than either amitriptyline or imipramine. The initial clinical effect may occur within four to seven days and occurs within 2 weeks in over 80% of responders.

INDICATIONS

ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions and depression accompanied by anxiety or agitation.

CONTRAINDICATIONS

Prior hypersensitivity to dibenzoxazepine compounds and in the acute recovery phase following myocardial infarction. Do not give concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. Before replacing a monoamine oxidase inhibitor with ASENDIN allow a minimum of 14 days to elapse, then initiate cautiously, with gradual increase in dosage until optimum response is achieved.

WARNINGS

Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (ie, antipsychotic) drugs. (Amoxapine is not an antipsychotic, but it has substantive neuroleptic activity.) Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on **Information for the Patient** and **ADVERSE REACTIONS.)**

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex, NMS has been reported in association with antipsychotic drugs. Clinical manifestations are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Diagnosis is complicated. Rule out serious medical illness (eg, pneumonia, systemic infection) and inadequately treated extrapyramidal symptoms (EPS). Other considerations in differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology. Management of NMS includes immediate discontinuation of antipsychotic and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of concomitant serious medical problems for which specific treatments are available. Reintroduction of antipsychotic drug treatment after recovery from NMS should be carefully considered and closely monitored since recurrences of NMS have been reported.

Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intraocular pressure. Watch patients with cardiovascular disorders closely. Tricyclic antidepressants, particularly in high doses, can induce sinus tachycardia, changes in conduction time, and arrhythmias. Myocardial infarction and stroke have been reported with drugs of this class. Take extreme caution in patients with history of convulsive disorders or those with overt or latent seizure disorders.

PRECAUTIONS

General: Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the drug. Manic depressive patients may experience a shift to the manic phase; schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have such symptoms exaggerated, requiring reduction of dosage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause skin rashes and/or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. ASENDIN *amoxapine* should be discontinued if rash and/or fever develop. Amoxapine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in <1% of patients. Rarely, symptoms indicative of tardive dyskinesia have been reported. **Information for the Patient:** It is advised that all patients in whom chronic use of neuroleptic drugs is contemplated be given full information about the risk of tardive dyskinesia. Warn patients of possibility of drowsiness; performance of potentially hazardous tasks such as driving an automobile or operating machinery may be impaired. **Drug Interactions:** See **CONTRAINDICATIONS** regarding concurrent usage of tricyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur when tricyclic antidepressants are taken in combination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when cimetidine is administered concurrently. Although such an interaction has not been reported to date with ASENDIN, specific interaction studies have not been done, and the possibility should be considered. **Therapeutic Interactions:** Concurrent administration with electroshock may increase hazards associated with such therapy. **Carcinogenesis, Impairment of Fertility:** In a 21-month toxicity study at three-dose levels in rats, pancreatic islet cell hyperplasia occurred with slightly increased incidence at doses 5-10 times the human dose. Pancreatic adenocarcinoma was detected in low incidence in the mid-dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length. **Pregnancy:** *Pregnancy Category C:* Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between days 0-4) was demonstrated in the offspring of rats at 5-10 times the human dose. There are no adequate and well-controlled studies of pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women. **Pediatric Use:** Safety and effectiveness in children below the age of 16 have not been established.

ADVERSE REACTIONS

Reported in Controlled Studies: **Incidence Greater than 1%:** Most frequent were sedative and anticholinergic: drowsiness (14%), dry mouth (14%), constipation (12%), and blurred vision (7%).

Less frequently reported reactions were: *CNS and Neuromuscular:* anxiety, insomnia, restlessness, nervousness, palpitations, tremors, confusion, excitement, nightmares, ataxia, alterations in EEG patterns. *Allergic:* edema, skin rash. *Endocrine:* elevation of prolactin levels. *Gastrointestinal:* nausea. *Other:* dizziness, headache, fatigue, weakness, excessive appetite, increased perspiration. **Incidence Less than 1%:** *Anticholinergic:* disturbances of accommodation, mydriasis, delayed micturition, urinary retention, nasal stuffiness. *Cardiovascular:* hypotension, hypertension, syncope, tachycardia. *Allergic:* drug fever, urticaria, photosensitization, pruritus, rarely, vasculitis, hepatitis. *CNS and Neuromuscular:* tingling, paresthesias of the extremities, tinnitus, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, extrapyramidal symptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported. (See **WARNINGS**.) *Hematologic:* leukopenia, agranulocytosis. *Gastrointestinal:* epigastric distress, vomiting, flatulence, abdominal pain, peculiar taste, diarrhea. *Endocrine:* increased or decreased libido, impotence, menstrual irregularity, breast enlargement, and galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion. *Other:* lacrimation, weight gain or loss, altered liver function, painful ejaculation. **Drug Relationship Unknown:** Reported rarely, but under circumstances where drug relationship was unknown: *Anticholinergic:* paralytic ileus. *Cardiovascular:* atrial arrhythmias (including atrial fibrillation), myocardial infarction, stroke, heart block. *CNS and Neuromuscular:* hallucinations. *Hematologic:* thrombocytopenia, eosinophilia, purpura, petechiae. *Gastrointestinal:* parotid swelling. *Endocrine:* change in blood glucose levels. *Other:* pancreatitis, hepatitis, jaundice, urinary frequency, testicular swelling, anorexia, alopecia. **Additional Adverse Reactions:** Reported with other antidepressant drugs, but not with ASENDIN. *Anticholinergic:* sublingual adenitis, dilation of the urinary tract. *CNS and Neuromuscular:* delusions. *Gastrointestinal:* stomatitis, black tongue. *Endocrine:* gynecomastia.

OVERDOSAGE

Signs and Symptoms: Toxic manifestations of ASENDIN overdosage differ significantly from those of other tricyclic antidepressants. Serious cardiovascular effects are seldom, if ever, observed. However, CNS effects—particularly grand mal convulsions—occur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitutes a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN overdosage in some cases. Renal failure may develop two to five days after toxic dosage, typically in those who have experienced multiple seizures. **Treatment:** Treatment of ASENDIN overdosage should be symptomatic and supportive, but with special attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, requires vigorous treatment such as that described by Delgado-Escueta, et al (*N Engl J Med* 1982; 306:1337-1340).

Convulsions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant medication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for nondrug-induced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdosage, and the ECG typically remains within normal limits, except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is *not* a useful guide to the severity of overdosage with this drug. Fatalities and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENDIN overdosage patients.

Rev. 11/87

1. Anton RF, Hitri A, Diamond BI, et al: Amoxapine treatment of psychotic depression: Dose effect and dopamine blockade. *J Clin Psychiatry Monograph* 1986;4:32-36.

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The Less Sedating Therapy for Tourette Syndrome

INDICATIONS AND USAGE

ORAP (pimozide) is indicated for the suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment. ORAP is not intended as a treatment of first choice nor is it intended for the treatment for tics that are merely annoying or cosmetically troublesome. ORAP should be reserved for use in Tourette's Disorder patients whose development and/or daily life function is severely compromised by the presence of motor and phonic tics.

Evidence supporting approval of pimozide for use in Tourette's Disorder was obtained in two controlled clinical investigations which enrolled patients between the ages of 8 and 53 years. Most subjects in the two trials were 12 or older.

CONTRAINDICATIONS

1. ORAP (pimozide) is contraindicated in the treatment of simple tics or tics other than associated with Tourette's Disorder.
2. ORAP should not be used in patients taking drugs that may, themselves, cause motor and phonic tics (e.g., pemoline, methylphenidate and amphetamines) until such patients have been withdrawn from these drugs to determine whether or not the drugs, rather than Tourette's Disorder, are responsible for the tics.
3. Because ORAP prolongs the QT interval of the electrocardiogram it is contraindicated in patients with congenital long QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which prolong the QT interval of the electrocardiogram (see DRUG INTERACTIONS).
4. ORAP is contraindicated in patients with severe toxic central nervous system depression or comatose states from any cause.
5. ORAP is contraindicated in patients with hypersensitivity to it. As it is not known whether cross-sensitivity exists among the antipsychotics, pimozide should be used with appropriate caution in patients who have demonstrated hypersensitivity to other antipsychotic drugs.

WARNINGS

The use of ORAP (pimozide) in the treatment of Tourette's Disorder involves different risk/benefit considerations than when antipsychotic drugs are used to treat other conditions. Consequently, a decision to use ORAP should take into consideration the following: (see also PRECAUTIONS–Information for Patients).

Tardive Dyskinesia A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to antipsychotic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS and PRECAUTIONS–Information for Patients.)

Neuroleptic Malignant Syndrome (NMS) A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperpyrexia, not associated with the above symptom complex, has been reported with other antipsychotic drugs.

Other Sudden, unexpected deaths have occurred in experimental studies of conditions other than Tourette's Disorder. These deaths occurred while patients were receiving dosages in the range of 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. An electrocardiogram should be performed before ORAP treatment is initiated and periodically thereafter, especially during the period of dose adjustment.

ORAP may have a tumorigenic potential. Based on studies conducted in mice, it is known that pimozide can produce a dose related increase in pituitary tumors. The full significance of this finding is not known, but should be taken into consideration in the physician's and patient's decisions to use this drug product. This finding should be given special consideration when the patient is young and chronic use of pimozide is anticipated. (see PRECAUTIONS–Carcinogenesis, Mutagenesis, Impairment of Fertility).

PRECAUTIONS

General ORAP (pimozide) may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy.

ORAP produces anticholinergic side effects and should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

ORAP should be administered cautiously to patients with impairment of liver or kidney function, because it is metabolized by the liver and excreted by the kidneys.

Antipsychotics should be administered with caution to patients receiving anticonvulsant medication, with a history of seizures, or with EEG abnormalities, because they may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be maintained concomitantly.

Laboratory Tests An ECG should be done at baseline and periodically thereafter throughout the period of dose adjustment. Any indication of prolongation of QT_C interval beyond an absolute limit of 0.47 seconds (children) or 0.52 seconds (adults), or more than 25% above the patient's original baseline should be considered a basis for stopping further dose increase (see CONTRAINDICATIONS) and considering a lower dose.

Since hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency, secondary to diuretics, diarrhea, or other cause, should be corrected before ORAP therapy is initiated and normal potassium maintained during therapy.

Drug Interactions Because ORAP prolongs the QT interval of the electrocardiogram, an additive effect on QT interval would be anticipated if administered with other drugs, such as phenothiazines, tricyclic antidepressants or antiarrhythmic agents, which prolong the QT interval. Such concomitant administration should not be undertaken (see CONTRAINDICATIONS).

ORAP may be capable of potentiating CNS depressants, including analgesics, sedatives, anxiolytics, and alcohol.

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity studies were conducted in mice and rats. In mice, pimozide causes a dose-related increase in pituitary and mammary tumors.

When mice were treated for up to 18 months with pimozide, pituitary gland changes developed in females only. These changes were characterized as hyperplasia at doses approximating the human dose and adenoma at doses about fifteen times the maximum recommended human dose on a mg per kg basis. The mechanism for the induction of pituitary tumors in mice is not known

Mammary gland tumors in female mice were also increased, but these tumors are expected in rodents treated with antipsychotic drugs which elevate prolactin levels. Chronic administration of an antipsychotic also causes elevated prolactin levels in humans. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with antipsychotic drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis. The available evidence, however, is considered too limited to be conclusive at this time.

In a 24 month carcinogenicity study in rats, animals received up to 50 times the maximum recommended human dose. No increased incidence of overall tumors or tumors at any site was observed in either sex. Because of the limited number of animals surviving this study, the meaning of these results is unclear.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains, in the mouse dominant lethal test or in the micronucleus test in rats.

Reproduction studies in animals were not adequate to assess all aspects of fertility. Nevertheless, female rats administered pimozide had prolonged estrus cycles, an effect also produced by other antipsychotic drugs.

Pregnancy Category C. Reproduction studies performed in rats and rabbits at oral doses up to 8 times the maximum human dose did not reveal evidence of teratogenicity. In the rat, however, this multiple of the human dose resulted in decreased pregnancies and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation which is also observed in rodents administered other antipsychotic drugs. In the rabbit, maternal toxicity, mortality, decreased weight gain, and embryotoxicity including increased resorptions were dose related. Because animal reproduction studies are not always predictive of human response, pimozide should be given to a pregnant woman only if the potential benefits of treatment clearly outweigh the potential risks.

Labor and Delivery This drug has no recognized use in labor or delivery.

Nursing Mothers It is not known whether pimozide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity and unknown cardiovascular effects in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use Although Tourette's Disorder most often has its onset between the ages of 2 and 15 years, information on the use and efficacy of ORAP in patients less than 12 years of age is limited.

Because its use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder.

ADVERSE REACTIONS

General: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions during the administration of ORAP (pimozide) have been reported frequently, often during the first few days of treatment. In most patients, these reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible.

Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently. Severe extrapyramidal reactions have been reported to occur at relatively low doses. Generally the occurrence and severity of most extrapyramidal symptoms are dose related since they occur at relatively high doses and have been shown to disappear or become less severe when the dose is reduced. Administration of antiparkinson drugs such as benztropine mesylate or trihexyphenidyl hydrochloride may be required for control of such reactions. It should be noted that persistent extrapyramidal reactions have been reported and that the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under "Tardive Dyskinesia" except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of ORAP.

Tardive Dyskinesia: ORAP may be associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop.

Electrocardiographic Changes: Electrocardiographic changes have been observed in clinical trials of ORAP in Tourette's Disorder and schizophrenia. These have included prolongation of the QT interval, flattening, notching and inversion of the T wave and the appearance of U waves. Sudden, unexpected deaths and grand mal seizure have occurred at doses above 20 mg/day

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome (NMS) has been reported with ORAP. (See WARNINGS for further information concerning NMS.)

Hyperpyrexia: Hyperpyrexia has been reported with other antipsychotic drugs.

Clinical Trials The following adverse reaction tabulation was derived from 20 patients in a 6 week long placebo controlled clinical trial of ORAP in Tourette's Disorder.

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Body as a Whole		
Headache	1	2
Gastrointestinal		
Dry mouth	5	1
Diarrhea	1	0
Nausea	0	2
Vomiting	0	1
Constipation	4	2
Eructations	0	1
Thirsty	1	0
Appetite increase	1	0
Endocrine		
Menstrual disorder	0	1
Breast secretions	0	1
Musculoskeletal		
Muscle cramps	0	1
Muscle tightness	3	0
Stooped posture	2	0
CNS		
Drowsiness	7	3
Sedation	14	5
Insomnia	2	2
Dizziness	0	1
Akathisia	8	0
Rigidity	2	0
Speech disorder	2	0
Handwriting change	1	0
Akinesia	8	0
Psychiatric		
Depression	2	3
Excitement	0	1
Nervous	1	0
Adverse behavior effect	5	0
Special Sense		
Visual disturbance	4	0
Taste change	1	0
Sensitivity of eyes to light	1	0
Decreased accommodation	4	1
Spots before eyes	0	1
Urogenital		
Impotence	3	0

Because clinical investigational experience with ORAP in Tourette's Disorder is limited, uncommon adverse reactions may not have been detected. The physician should consider that other adverse reactions associated with antipsychotics may occur.

Other Adverse Reactions In addition to the adverse reactions listed above, those listed below have been reported in U.S. clinical trials of ORAP in conditions other than Tourette's Disorder.

Body as a Whole: Asthenia, chest pain, periorbital edema

Cardiovascular/Respiratory: Postural hypotension, hypotension, hypertension, tachycardia, palpitations

Gastrointestinal: Increased salivation, nausea, vomiting, anorexia, GI distress

Endocrine: Loss of libido

Metabolic/Nutritional: Weight gain, weight loss

Central Nervous System: Dizziness, tremor, parkinsonism, fainting, dyskinesia

Psychiatric: Excitement

Skin: Rash, sweating, skin irritation

Special Senses: Blurred vision, cataracts

Urogenital: Nocturia, urinary frequency

Postmarketing Reports The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ORAP.

Hematologic: Hemolytic anemia

OVERDOSAGE

In general, the signs and symptoms of overdosage with ORAP (pimozide) would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) electrocardiographic abnormalities, 2) severe extrapyramidal reactions, 3) hypotension, 4) a comatose state with respiratory depression.

In the event of overdosage, gastric lavage, establishment of a patent airway and, if necessary mechanically-assisted respiration are advised. Electrocardiographic monitoring should commence immediately and continue until the ECG parameters are within the normal range. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. Because of the long half-life of pimozide, patients who take an overdose should be observed for at least 4 days. As with all drugs, the physician should consider contacting a poison control center for additional information on the treatment of overdose.

DOSAGE AND ADMINISTRATION

Reliable dose response data for the effects of ORAP (pimozide) on tic manifestations in Tourette's Disorder patients below the age of twelve are not available. Consequently, the suppression of tics by ORAP requires a slow and gradual introduction of the drug. The patient's dose should be carefully adjusted to a point where the suppression of tics and the relief afforded is balanced against the untoward side effects of the drug.

An ECG should be done at baseline and periodically thereafter, especially during the period of dose adjustment (see WARNINGS and PRECAUTIONS–Laboratory Tests).

In general, treatment with ORAP should be initiated with a dose of 1 to 2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg per day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended.

Periodic attempts should be made to reduce the dosage of ORAP to see whether or not tics persist at the level and extent first identified. In attempts to reduce the dosage of ORAP, consideration should be given to the possibility that increases of tic intensity and frequency may represent a transient, withdrawal related phenomenon rather than a return of disease symptoms. Specifically, one to two weeks should be allowed to elapse before one concludes that an increase in tic manifestations is a function of the underlying disease syndrome rather than a response to drug withdrawal. A gradual withdrawal is recommended in any case.

HOW SUPPLIED

ORAP (pimozide) 2 mg tablets, white, scored, imprint "LEMMON" and "ORAP 2"–NDC 0093-0187-01, bottles of 100.

Dispense in tight, light-resistant containers as defined in the official compendium.

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Printed in USA
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1. Shapiro AK et al: *Pediatrics* 79:1032-1038, 1987.
2. Ross MS et al: *Am J Psychiatry* 135:585-587, 1978.

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Please see brief summary of SINEQUAN® (doxepin HCl) prescribing information on next page.

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References: 1. Goldberg HL: Sleep disturbance as a manifestation of depression, in *Somatic Depression: Insights for Primary Care Physicians*. Proceedings of a symposium held in Miami, Dec 4, 1978. New York, Postgraduate Medicine Communications, pp 13-18. **2.** Karacan I, Blackburn AB, Thornby JI, et al: The effect of doxepin HCl (Sinequan) on sleep patterns and clinical symptomatology of neurotic depressed patients with sleep disturbance, in *Sinequan® (doxepin HCl): A Monograph of Recent Clinical Studies*. Princeton, NJ, Excerpta Medica, 1977, pp 4-22. **3.** Goldberg HL, Finnerty RJ: The use of doxepin in the treatment of symptoms of anxiety neurosis and accompanying depression: A collaborative controlled study. *Am J Psychiatry* 1972;129(July):74-77.

SINEQUAN® (doxepin HCl)

BRIEF SUMMARY
SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There has been a report of apnea and drowsiness occurring in a nursing infant whose mother was taking SINEQUAN.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

Drug Interactions.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Cimetidine: Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants. Serious anticholinergic symptoms (i.e., severe dry mouth, urinary retention and blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressant when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been observed when they are begun in patients already taking cimetidine. In patients who have been reported to be well controlled on tricyclic antidepressants receiving concurrent cimetidine therapy, discontinuation of cimetidine has been reported to decrease established steady-state serum tricyclic anti depressant levels and compromise their therapeutic effects.

Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Tolazamide: A case of severe hypoglycemia has been reported in a type II diabetic patient maintained on tolazamide (1 gm/day) 11 days after the addition of doxepin (75 mg/day).

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN (doxepin HCl).

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, extrapyramidal symptoms, seizures, tardive dyskinesia, and tremor.

Cardiovascular: Cardiovascular effects including hypotension, hypertension, and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone secretion have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, headache, exacerbation of asthma, and hyperpyrexia (in association with chlorpromazine) have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

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Please see a summary of product information on adjacent page.

VALIUM® (diazepam/Roche) ⒸIV

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATED: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

WARNINGS: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

PRECAUTIONS: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear. Inform patients to consult physician before increasing dose or abruptly discontinuing diazepam.

SIDE EFFECTS: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of diazepam; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

DOSAGE: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

HOW SUPPLIED: For oral administration, round, scored tablets with a cut out "V" design—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100 and 500. Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10.

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20-mg once-a-day therapy

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1. *Curr Ther Res* 1986;39:559–563.
*As defined by DSM-III.

See adjacent page for brief summary of prescribing information.

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Prozac®

fluoxetine hydrochloride

Brief Summary: Consult the package literature for complete prescribing information.

Indication: Prozac is indicated for the treatment of depression.

Contraindication: Prozac is contraindicated in patients known to be hypersensitive to it.

Warnings: *Monoamine Oxidase Inhibitors* – Data on the effects of the combined use of fluoxetine and MAO inhibitors are limited. Their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI. Administration of an MAOI within five weeks of discontinuation of fluoxetine may increase the risk of serious events. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine.

Rash and Accompanying Events – During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknowable at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: *General* – Anxiety and Insomnia – Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight – Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with Prozac compared to 4% of placebo- and 3% of tricyclic-antidepressant-treated patients. However, only rarely have patients been discontinued from treatment with Prozac because of weight loss.

Activation of Mania/Hypomania – During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures – Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide – The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites – Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (*see* Clinical Pharmacology *and* Dosage and Administration).

Use in Patients With Concomitant Illness – Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has **not** been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference With Cognitive and Motor Performance – Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients – Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests – There are no specific laboratory tests recommended.

Drug Interactions – As with all drugs, the potential for interaction by a variety of mechanisms (ie, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc) is a possibility (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Tryptophan – Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors – *See* Warnings.

Other Antidepressants – There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Diazepam Clearance – The half-life of concurrently administered diazepam may be prolonged in some patients (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins – Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

CNS-Active Drugs – The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Electroconvulsive Therapy – There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility – There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy – Teratogenic Effects – Pregnancy Category B – Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery – The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers – It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children – Safety and effectiveness in children have not been established.

Usage in the Elderly – Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Hyponatremia – Several cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

Adverse Reactions: *Commonly Observed* – The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment – Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

TABLE 1. TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

	Percentage of Patients Reporting Event	
Body System/ Adverse Event*	Prozac (N=1,730)	Placebo (N=799)
Nervous		
Headache	20.3	15.5
Nervousness	14.9	8.5
Insomnia	13.8	7.1
Drowsiness	11.6	6.3
Anxiety	9.4	5.5
Tremor	7.9	2.4
Dizziness	5.7	3.3
Fatigue	4.2	1.1
Sedated	1.9	1.3
Sensation disturbance	1.7	2.0
Libido, decreased	1.6	–
Light-headedness	1.6	–
Concentration, decreased	1.5	–
Digestive		
Nausea	21.1	10.1
Diarrhea	12.3	7.0
Mouth dryness	9.5	6.0
Anorexia	8.7	1.5
Dyspepsia	6.4	4.3
Constipation	4.5	3.3
Pain, abdominal	3.4	2.9
Vomiting	2.4	1.3
Taste change	1.8	–
Flatulence	1.6	1.1
Gastroenteritis	1.0	1.4
Skin and Appendages		
Sweating, excessive	8.4	3.8
Rash	2.7	1.8
Pruritus	2.4	1.4
Body as a Whole		
Asthenia	4.4	1.9
Infection, viral	3.4	3.1
Pain, limb	1.6	1.1
Fever	1.4	–
Pain, chest	1.3	1.1
Allergy	1.2	1.1
Influenza	1.2	1.5
Respiratory		
Upper respiratory infection	7.6	6.0
Flu-like syndrome	2.8	1.9
Pharyngitis	2.7	1.3
Nasal congestion	2.6	2.3
Headache, sinus	2.3	1.8
Sinusitis	2.1	2.0
Cough	1.6	1.6
Dyspnea	1.4	–
Cardiovascular		
Hot flushes	1.8	1.0
Palpitations	1.3	1.4
Musculoskeletal		
Pain, back	2.0	2.4
Pain, joint	1.2	1.1
Pain, muscle	1.2	1.0
Urogenital		
Menstruation, painful	1.9	1.4
Sexual dysfunction	1.9	–
Frequent micturition	1.6	–
Urinary tract infection	1.2	–
Special Senses		
Vision disturbance	2.8	1.8

*Events reported by at least 1% of Prozac-treated patients are included.
– Incidence less than 1%.

Incidence in Controlled Clinical Trials – Table 1 enumerates adverse events that occurred at a frequency of 1% or more among Prozac-treated patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Other Events Observed During the Premarketing Evaluation of Prozac – During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 individuals exposed to Prozac who experienced an event of the type cited on at least one occasion while receiving Prozac. All reported events are included except those already listed in tables, those COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole – *Frequent:* chills; *Infrequent:* chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; *Rare:* abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System – *Infrequent:* angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; *Rare:* AV block (first-degree), bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System – *Frequent:* increased appetite; *Infrequent:* aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, and thirst; *Rare:* bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

Endocrine System – *Infrequent:* hypothyroidism; *Rare:* goiter and hyperthyroidism.

Hemic and Lymphatic System – *Infrequent:* anemia and lymphadenopathy; *Rare:* bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocythemia.

Metabolic and Nutritional – *Frequent:* weight loss; *Infrequent:* generalized edema, hypoglycemia, peripheral edema, and weight gain; *Rare:* dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficiency anemia.

Musculoskeletal System – *Infrequent:* arthritis, bone pain, bursitis, tenosynovitis, and twitching; *Rare:* bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System – *Frequent:* abnormal dreams and agitation; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System – *Frequent:* bronchitis, rhinitis, and yawn; *Infrequent:* asthma, epistaxis, hiccup, hyperventilation, and pneumonia; *Rare:* apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, and pleural effusion.

Skin and Appendages – *Infrequent:* acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; *Rare:* eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses – *Infrequent*: amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; *Rare:* blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System – *Infrequent:* abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; *Rare:* abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postintroduction Reports – Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: vaginal bleeding after drug withdrawal, hyperprolactinemia, and thrombocytopenia.

Overdosage: *Human Experience* – As of December 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L respectively. A second death involved three drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.80 mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (*see* Management of Overdose). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without residua.

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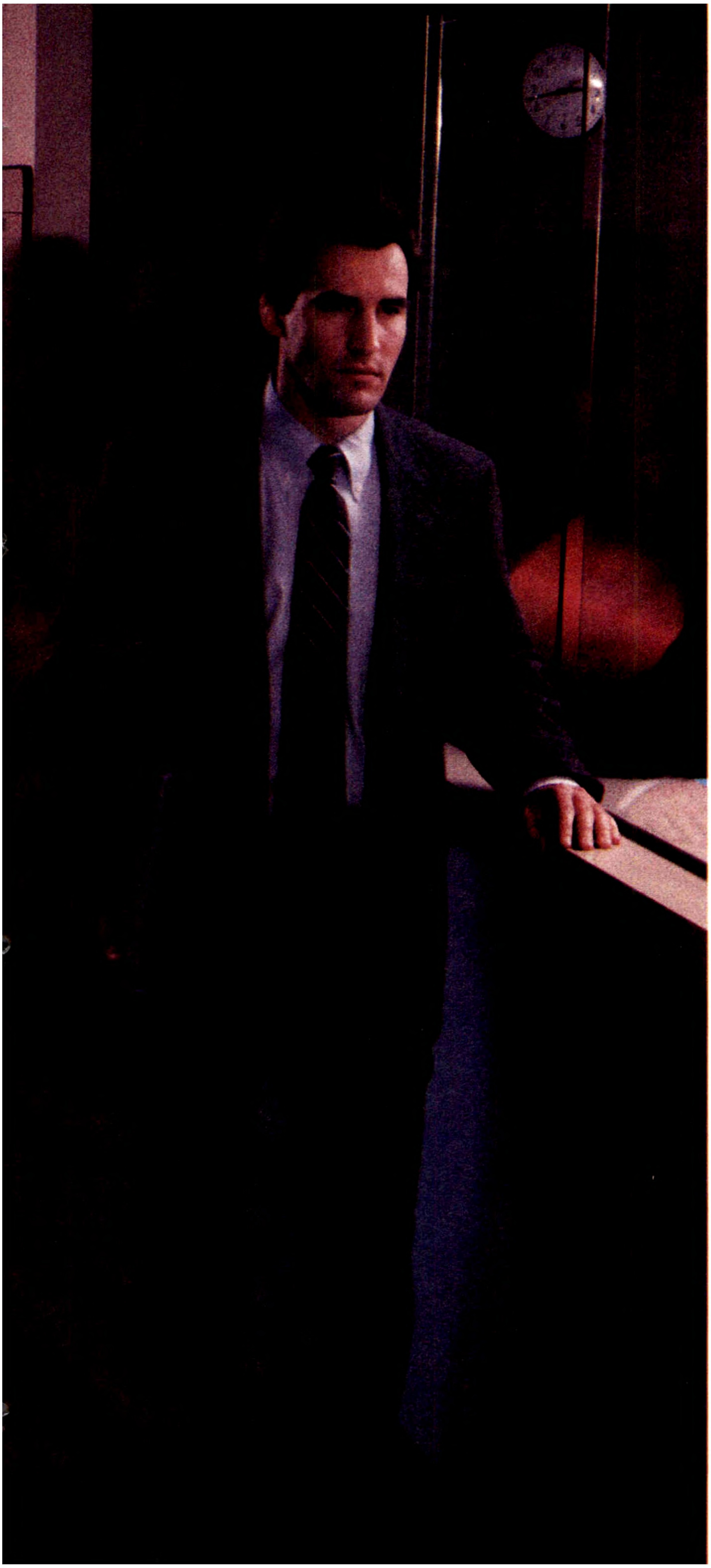

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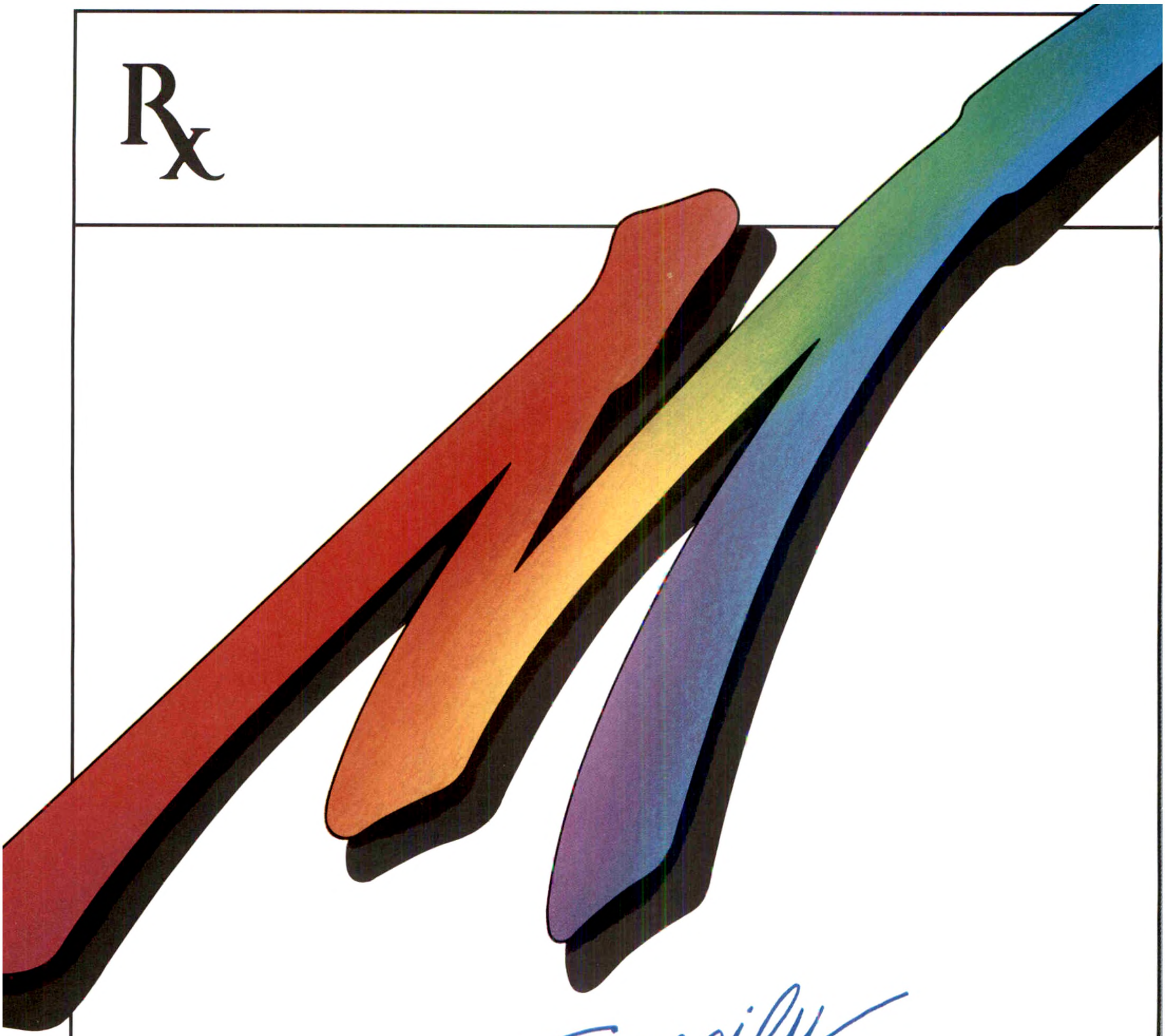

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THE AMERICAN JOURNAL OF PSYCHIATRY

Editorial

The Chronically Mentally Ill, Residency Training, and Psychiatry

The care of the chronically mentally ill has challenged the skills of mental health professionals as well as frustrated and taxed the resources of society. This is the case now and has been the case for many centuries, at least since the medieval days of the ships of fools. Whatever new treatment and seemingly revolutionary or innovative interventions are developed, whether asylums, psychopharmacology, or community treatment, the end result inexorably remains the same—the chronically mentally ill are abandoned, rejected, and neglected—in other words, they are jailed, warehoused in snake pits, or homeless.

Somehow, our society is not prepared to commit adequate resources, and it lacks the inner moral authority to ensure that those who are psychologically impaired will be given more than a modicum of food and clothing. There appears to be a denial of the suffering experienced by those patients and a tacit wish to perceive the homeless schizophrenic individual as exercising a right to be different! As our society is confronted—in fact, it can be argued, overwhelmed—by the epidemic of drug use, crime, and homelessness, the legal system appears to be more concerned about iatrogenic effects of medications and the possible abridgment of civil rights rather than the horrible consequences of mental illness.

The chronically mentally ill patient is of a different mold than the chronic hypertensive or arthritic patient, and his or her care requires a comprehensive system of psychiatric, psychosocial, and inpatient as well as day treatment rehabilitative services, with decent housing that is protected and immune from the enticements of street drugs and sufficiently sheltered to minimize external stress. This means a system in which the whole is much greater than the sum of the parts, in fact, an extramural therapeutic milieu. In such a system psychiatry is only a part, but a vital part, of the provision of care. Such a system is also expensive. In this day and age of escalating health care costs and heroic but futile attempts to cap them, one can understand why society may, in fact, deliberately ignore a large segment of its citizens who, because of their pathology, are noncompliant with the available resources, which, however inadequate, are already expensive.

Anything that throws light on the plight of the chronically mentally ill, as well as the suffering experienced by the families, and any intervention that may facilitate rehabilitation or at least a stabilization of the impairment deserve our professional support and encouragement. The article by Faulkner et al., a group of eminent psychiatric educators, elsewhere in this issue discusses only one aspect of the problem. It is important to emphasize what it does not address to be able to appreciate what it does propose. The suggestions are not intended to, nor will, address the care of the chronically mentally ill, nor do the authors imply that the proposed curriculum enrichment would in itself track more psychiatrists to the public psychiatry sector. But the proposals will enrich the new psychiatrist's understanding of the major social, family, and community aspects of the chronically mentally ill. That is a positive step, since most of the prestigious training programs are based in acute care institutions and their alumni often have only limited exposure to chronic patients except possibly in emergency rooms, where such patients are also perceived as noncompliant public nuisances.

The proposals address and suggest options that will allow the trainee to obtain an appropriate supervised experience. As one would expect from a group of educators, the evaluation of such an educational experience is well thought out, although the details and the ultimate goals are left to the discretion and local resources of each training program. Training directors are not in a position to change the reality of their world, and the proposals are consistent with *essentials* of psychiatric training and well within the realistic limits of most psychiatric programs. The proposals can be customized to local needs and resources.

The proposals, while limited, will demand extra commitment of time from trainee and educators alike. This poses logistic difficulties, since schedules and rotations are tight, but even more challenging will be finding the money to pay for the stipends for what is primarily an educational experience and not a service function. Residencies continue to be neither fish nor fowl, i.e., remunerated by hospitals for service provided and not fellowship stipends for study.

The presence of psychiatrists in private practice or academia who are better informed and more sophisticated regarding these issues will not address the recidivism, the homeless mentally ill, or the explosive and impulsive patient who at times terrifies the family and continuously causes serious emotional harm. The sensible proposals by Faulkner et al. will not address these problems, since there is a dearth of public psychiatry programs that would appeal to and attract trainees to public psychiatry. (The notable exceptions are cited in their article.) Psychiatry will not by itself be in a position to change the situation. Professionals, however motivated by their social conscience, are not Don Quixotes and will not fight the windmills of entrenched social apathy or firmly held social beliefs, however erroneous or seemingly misguided.

But organized psychiatry needs to be reminded of our specialty's historical roots, which are in the public sector. Psychiatry's antecedents were in the area of public health, an identity that was shed and forgotten in the halcyon days of psychoanalysis, a process followed by the medicalization of psychiatry as a result of psychopharmacological breakthroughs. It may be a truism, but it needs to be repeated that we do not have to give up our recently acquired scientific and biological sophistication to be involved in social psychiatry. The exposure of the resident to the care of the chronically mentally ill patient will keep the torch of continued concern and social awareness.

Clearly, what is available is not enough. What is being urged will not suffice. The mentally ill exist in large numbers, and their plight cries out for a modern Dorothea Dix. If our professional society cannot meet their need, it will not be surprising, and in time it will be inevitable, that the public sector will become the sole domain of the clinical psychologist and social worker. Nature abhors a vacuum, and the care of the chronically mentally ill is a societal vacuum. Faulkner and associates are to be commended for their suggestions; these suggestions should be implemented as much as possible so that psychiatry stays involved in this social problem. This is not a question of turf issues or of competition for dwindling resources; it should be seen as an expression of pride in the knowledge base that psychiatry has developed over many centuries. Such curriculum enrichment may stimulate other state mental health systems and psychiatry training programs to emulate the few leaders in this field.

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Second Messenger Systems and Psychoactive Drug Action: Focus on the Phosphoinositide System and Lithium

Jay M. Baraban, M.D., Ph.D., Paul F. Worley, M.D., and Solomon H. Snyder, M.D.

Most models of psychotropic drug action have emphasized effects on the release or uptake of neurotransmitters as well as interactions with receptors. Stimulation of neurotransmitter receptors triggers a complex array of electrical and biochemical actions. Recent experimental advances have greatly clarified the second messenger systems underlying neurotransmitter actions, suggesting novel sites of action for psychotropic agents. The authors emphasize the phosphoinositide system and the implications of its involvement for the therapeutic actions of lithium.

(Am J Psychiatry 1989; 146:1251–1260)

Most of the major drugs used in psychiatry were introduced some 3 decades ago. In intervening years much progress has been made in understanding their mode of action in eliciting both therapeutic and side effects. Essentially all of the known actions of psychotropic drugs involve a handful of neurotransmitter systems. Specific sites of action vary among the different drugs: influences are exerted on metabolic enzymes, storage processes in synaptic vesicles, release mechanisms, and neurotransmitter receptors. Thus, reserpine depletes biogenic amines from the brain by impairing their storage in synaptic vesicles. Monoamine oxidase inhibitors block a key metabolic enzyme. Amphetamines enhance the release of catecholamines, and nearly all tricyclic antidepressants inhibit the reuptake inactivation of biogenic amines.

During the past 15 years, the ability to measure drug and neurotransmitter receptors by simple binding techniques (first developed for studies of opiate receptors) has helped clarify actions of numerous drugs (1). Blockade of the D_2 subtype of dopamine receptors may account for the therapeutic action of a wide range of antipsychotic agents (2, 3). The same drugs appear to exert their sedative effects by blocking α_1 adrenoceptors (4). The tendency of drugs in this group to elicit extrapyramidal side effects varies inversely with their muscarinic cholinergic antagonist potency (5). Psychedelic drugs appear to act primarily by mimicking serotonin at one class of serotonin receptors, the 5-HT_2 subtype (6–8).

Recently, increased attention has been devoted to amino acid neurotransmitters as sites of psychotropic drug action. Benzodiazepines have long been known to act by facilitating synaptic effects of γ-aminobutyric acid (GABA) (9). This action involves subtle interactions between subunits of the GABA receptor that have been characterized in detail by molecular cloning studies (10). GABA and benzodiazepines bind to different sites and possibly different subunits of the receptor protein. The binding of benzodiazepines increases the ability of GABA to interact with its recognition site. Barbiturates, meprobamate, and alcohol all appear to act through the GABA receptor protein complex but at different sites than the benzodiazepines or GABA itself. In contrast to these sedating and anticonvulsant drugs, agents that block GABA receptors cause excitation and convulsions. This is true for bicuculline, which blocks the GABA recognition site. The convulsant picrotoxin

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blocks GABA transmission but not at the GABA recognition site. Instead, picrotoxin acts at a site related to the chloride ion channel portion of the GABA receptor protein. GABA exerts its inhibitory, hyperpolarizing synaptic effects by opening chloride ion channels in synaptic membranes. Interestingly, the chloride ion channel is part of the same receptor protein complex as the GABA recognition site. Molecular cloning studies have shown that the nicotinic acetylcholine receptor and its associated cation channel are also part of the same protein complex (11) as the inhibitory glycine receptor and its chloride ion channel (12).

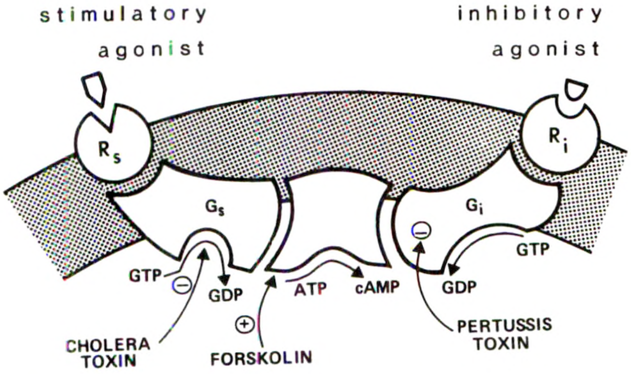
These GABA, glycine, and acetylcholine receptors represent a group of neurotransmitter receptors that directly influence ion channels. Many other neurotransmitters, perhaps the majority of the biogenic amines and neuropeptides, act through biochemical second messenger systems that enzymatically amplify the signal generated by the neurotransmitter-receptor binding events. Following a chain of molecular events, neurotransmitters that act through these second messengers may ultimately open or close ion channels in the plasma membrane or influence neuronal excitability through other intracellular metabolic events. During the past 15 years, neurotransmitter receptors have been extensively characterized at a molecular level and the drug actions mediated by these receptors have been thoroughly explored. Recent progress in understanding second messenger systems has clarified our understanding of neurotransmitter actions and focused attention on these systems as sites of psychotropic drug action.

This review will emphasize the phosphoinositide system, a major second messenger system in the brain, which has been extensively elucidated only in the last few years and which may be involved in the therapeutic actions of lithium. To introduce several general features of second messenger systems we will also outline briefly the organization of the cAMP system and focus on the role of GTP binding proteins that form the interface between transmitter receptors and both the phosphoinositide and cAMP systems.

cAMP AND GTP BINDING PROTEINS

Second messenger systems are triggered by neurotransmitter receptor stimulation (see figure 1). The transmitter-receptor complex then interacts with a GTP binding protein, usually designated as a G-protein. Interaction of the G-protein with the receptor increases its affinity for GTP. For the cAMP system, activation of the G-protein in this manner enables it to dissociate from the receptor and stimulate the enzyme adenylate cyclase, enhancing synthesis of cAMP from ATP. In turn, cAMP activates a phosphorylating enzyme called cAMP-dependent protein kinase or simply protein kinase A. This kinase then phosphorylates a wide range of substrate proteins that regulate diverse cellular functions.

FIGURE 1. Bidirectional Regulation of Adenylate Cyclase[a]



[a] A stimulatory agonist is recognized by a receptor (R_s), and together they activate the stimulatory GTP-binding regulatory unit for adenylate cyclase (G_s). Activation of G_s is associated with its binding of GTP, which displaces GDP. A parallel system is shown as inhibiting adenylate cyclase by activating the inhibitory regulatory unit for adenylate cyclase (G_i). Cholera toxin blocks the GTPase activity of G_s, causing its persistent activation. Pertussis toxin blocks the inhibitory action of G_i. At low concentrations, forskolin enhances the stimulatory interaction of G_s and adenylate cyclase; at higher concentrations, forskolin directly activates adenylate cyclase.

Some transmitters, such as catecholamines acting at β-adrenoceptors, stimulate adenylate cyclase, while others, such as enkephalin acting at opiate receptors, inhibit the enzyme. Distinct G-proteins mediate these two effects, G_s for stimulation and G_i for inhibition of adenylate cyclase (13). These differential effects involve the subunits of G-proteins. G-proteins consist of three subunits, designated alpha, beta, and gamma (14). Adenylate cyclase is directly activated by the alpha subunit of G_s. When alpha is bound to beta and gamma subunits, the G-protein is inactive. When the transmitter-receptor complex binds to the G-protein, GTP is enabled to interact potently with the G-protein, triggering dissociation of the beta and gamma subunits from the G_s protein. The resultant free alpha subunit then activates adenylate cyclase. At this point the alpha subunit, which also possesses intrinsic GTPase activity, cleaves GTP to GDP, whereupon the beta and gamma subunits reassociate with the alpha subunit, terminating activation of adenylate cyclase.

The way in which G_i inhibits adenylate cyclase has not been established definitively. However, one prominent model suggests that the initial events parallel activation of G_s and that the beta and gamma subunits dissociate from the alpha subunit when neurotransmitter receptor activation takes place. However, since the concentration of G_i is substantially greater than G_s, the beta and gamma subunits released from G_i are free to complex with the alpha subunit of G_s, preventing it from stimulating adenylate cyclase. Thus, transmitters that inhibit adenylate cyclase may do so indirectly, by preventing the activation of the enzyme by G_s. Another model suggests that the alpha subunit of G_i directly inhibits adenylate cyclase (14).

Besides regulating adenylate cyclase activity, G-proteins can directly influence ion channels. In the heart, acetylcholine through muscarinic receptors slows pacemaker cell firing by opening potassium channels. Patch-clamp recordings of individual potassium channels in the heart indicate that a unique G-protein, designated G_k, opens potassium channels without any other intervening metabolic steps (15, 16). Similarly, G-proteins may directly affect calcium channels in certain cell types in the dorsal root ganglion (17, 18). The alpha subunit of the G-protein is thought to interact with the ion channels and the beta and gamma subunits are thought to serve only to inactivate alpha subunits. However, some recent studies suggested that beta subunits can themselves have direct messenger functions at potassium channels (19) or at the prostaglandin precursor, forming enzyme phospholipase A_2 (20).

Besides the three G-proteins already mentioned (G_s, G_i, and G_k), molecular cloning techniques have revealed at least four others and many more may exist (21). One reason researchers formerly doubted the feasibility of drugs targeted at second messenger systems is that only a few principal second messenger systems have been identified, in contrast to the hundred or more distinct neurotransmitters and receptors. If only two or three second messenger systems mediate the bulk of neurotransmitter actions, drugs acting through second messengers might exert diffuse, global effects that would not be therapeutically useful. However, the considerable heterogeneity of the G-proteins and other aspects of second messengers suggest that selective drugs can be developed.

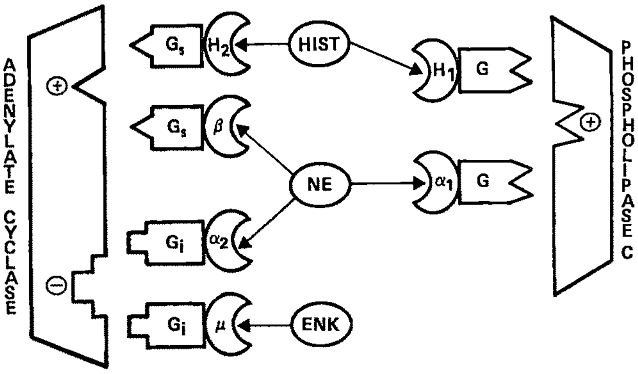
Improved understanding of the different G-proteins may indicate how they affect different brain functions discretely. The three best studied G-proteins in the brain are G_s, G_i, and G_o, a protein whose function is not yet known. Although G_s has been best characterized, it is least abundant, present at only half the levels of G_i and one-tenth the levels of G_o (22). Discrete localizations throughout the brain of G-proteins and other components of second messenger systems, to be discussed below, have considerably clarified these functions.

Although no therapeutic drugs have yet emerged in the cAMP system, some agents provide useful research probes. Forskolin is an alkaloid extracted from an Indian herb, *Coleus forskohlii,* which has been used for centuries to treat heart disease, insomnia, and convulsions. Forskolin potently activates adenylate cyclase (23), so that biological functions influenced by forskolin are candidates for being mediated by cAMP. Cholera toxin irreversibly activates adenylate cyclase by selectively modifying G_s enzymatically. By contrast, pertussis toxin selectively modifies G_i and G_o but not G_s (14).

THE PHOSPHOINOSITIDE SYSTEM

In contrast to the more than three decades of research on the cAMP system, the phosphoinositide cycle has been widely appreciated as a major second messenger system only in the past 5 years (24–26). The two systems display several similarities. They both work through G-proteins as well as phosphorylating enzymes. Both display considerable heterogeneity in their individual molecular components, so that subtle regulation in discrete parts of the brain are achievable.

FIGURE 2. The Multiple Actions of Individual Neurotransmitters on Second Messenger Systems[a]

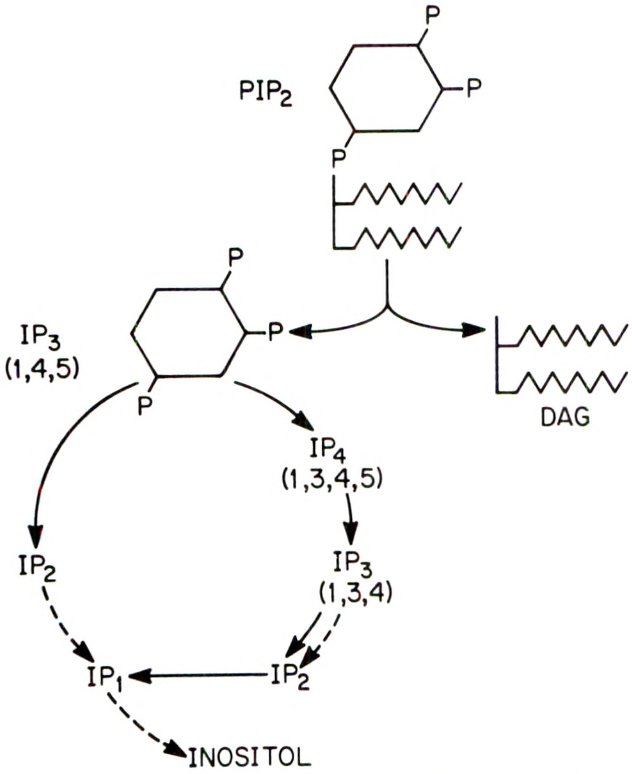


[a] These actions are carried out by their receptor subtypes, which are coupled with specific G-proteins. Histamine (HIST) stimulates adenylate cyclase by acting at H_2 receptors coupled to its stimulatory G-protein (G_s). Histamine also stimulates phospholipase C of the phosphoinositide second messenger system by acting at H_1 receptors linked to a distinct G-protein. Similarly, norepinephrine (NE) can stimulate (β receptor) or inhibit (α_2 receptor) adenylate cyclase or stimulate (α_1 receptor) phospholipase C. Conversely, each G-protein pool is coupled to several receptor subtypes: G_s is coupled to H_2 and β receptors, and the inhibitory G-protein for adenylate cyclase (G_i) is coupled to α_2 receptors and μ-opiate receptors (one of the enkephalin [ENK] receptor subtypes). An as yet unidentified G-protein (G) couples H_1 receptors and α_1 receptors to phospholipase C.

A variety of receptors can trigger the phosphoinositide cycle. It is difficult to tabulate those neurotransmitters which act through adenylate cyclase versus those which act through phosphoinositides because most neurotransmitters act through both. The discrimination comes in the receptor subtypes involved. For instance, norepinephrine acting at β-adrenoceptors stimulates adenylate cyclase, but norepinephrine inhibits the enzyme through α_2 adrenoceptors and stimulates the phosphoinositide cycle through α_1 receptors (see figure 2).

Receptor stimulation activates a phospholipase C enzyme selective for phosphatidylinositol and phosphorylated derivatives of this lipid. Phosphatidylinositol, which contains one phosphate group, is a major component of cell membranes. The phospholipid that appears to play a more prominent role as a second messenger contains an additional two phosphate groups and is termed phosphatidylinositol-bis-phosphate (PIP_2) (see figures 3 and 4). Phospholipase C triggers the breakdown of PIP_2 to the sugar phosphate inositol trisphosphate (IP_3), which contains the three phosphate groups of PIP_2. The other product of phospholipase activity is diacylglycerol (DAG). This action

FIGURE 3. Inositol Phosphate Metabolism[a]

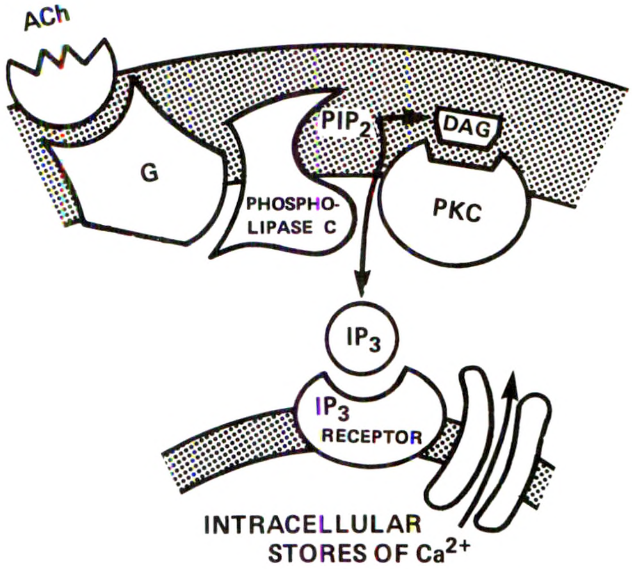


[a] Phosphatidylinositol-bis-phosphate (PIP$_2$) is hydrolyzed by phospholipase C, generating diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP$_3$[1,4,5]). IP$_3$(1,4,5) is acted on by either a kinase or a phosphatase, generating 1,3,4,5-tetrakisphosphate (IP$_4$[1,3,4,5]) or inositol 1,4-bis-phosphate (IP$_2$[1,4]), respectively. IP$_4$ (1,3,4,5) is hydrolyzed to IP$_3$(1,3,4) and then to IP$_2$. Specific phosphatases hydrolyze the various IP$_2$ isomers to inositol. Several inositol phosphatases are inhibited by lithium. These are shown as dotted arrows. In some steps both lithium-sensitive and lithium-insensitive enzymes are involved (27) so both solid and dotted arrows are shown.

of phospholipase C requires a G-protein whose identity has not yet been established definitively.

Both IP$_3$ and DAG influence cellular function in major ways. IP$_3$ binds to a unique receptor on the endoplasmic reticulum within the cell to trigger the release of calcium, which in turn can regulate cell function in many different ways. Thus, the IP$_3$ receptor is thought to be a crucial final common pathway for the phosphoinositide cycle. The IP$_3$ receptor represents a novel extension of the "receptor" concept because it is an intracellular recognition site in a second messenger system rather than a binding site for a neurotransmitter localized to the external surface of the plasma membrane. We (28, 29) and others (30) have been able to label IP$_3$ receptors through the binding of radiolabeled IP$_3$. We have purified the IP$_3$ receptor protein to homogeneity (31). The IP$_3$ receptor is a large protein comprising four identical subunits each of a molecular weight of about 260,000 daltons so that the full protein has a molecular weight greater than 1,000,000 daltons. When it occurs in intact membranes, binding of IP$_3$ to its receptors is potently inhibited by calcium in the submicromolar concentrations that normally occur within cells (see figure 5). This suggests a feedback mechanism whereby calcium released by IP$_3$ acts back on the IP$_3$ receptor to block further calcium release. The ability of calcium to inhibit IP$_3$ binding is mediated by a protein that is distinct from the IP$_3$ receptor, designated "calmedin" (32). We suspect that calmedin may be an important intracellular protein regulating numerous actions of calcium, perhaps in ways similar to the well-characterized calcium binding protein calmodulin.

FIGURE 4. Receptor-Mediated Phosphoinositide Turnover[a]

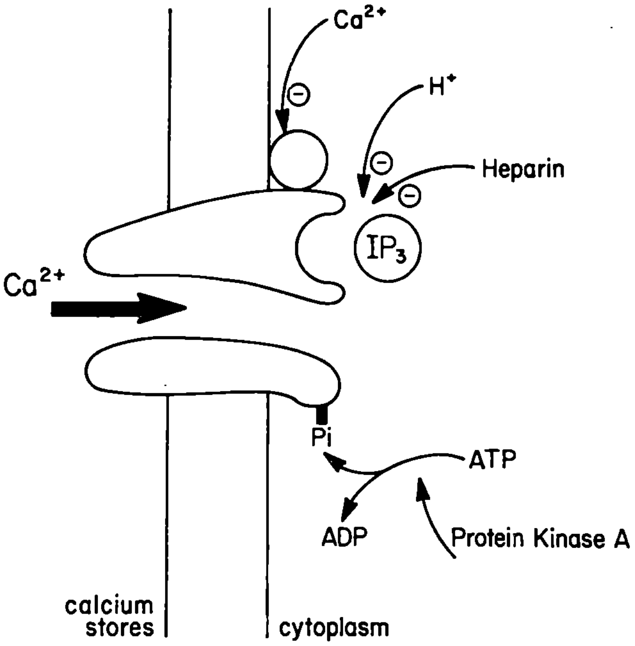


[a] A transmitter such as acetylcholine (ACh) binds to its receptor, which in turn activates a G-protein (G). Activated G-protein stimulates phospholipase C, which hydrolyzes phosphatidylinositol-bis-phosphate (PIP$_2$), generating inositol trisphosphate (IP$_3$) and diacylglycerol (DAG). IP$_3$ interacts with a specific receptor and causes the release of nonmitochondrial intracellular stores of calcium. DAG activates protein kinase C (PKC), which phosphorylates a broad range of substrates. Like DAG, phorbol esters activate PKC.

The IP$_3$ receptor is selectively phosphorylated by cAMP-dependent protein kinase decreasing the potency of IP$_3$ in releasing calcium (33). This suggests a specific mechanism for "cross talk" between the cAMP and the phosphoinositide second messenger systems. In other words, cAMP formed in response to neurotransmitter action would modulate the actions of transmitters that act through the phosphoinositide system by phosphorylating the IP$_3$ receptor and altering its function.

IP$_3$ formed by hydrolysis of PIP$_2$ can be phosphorylated further to inositol 1,3,4,5-tetrakisphosphate (IP$_4$) (34, 35). The exact function of IP$_4$ is not as well characterized as that of IP$_3$. IP$_4$ may facilitate the entry of calcium into the cell through the plasma membrane possibly directly into a pool of calcium that is susceptible to release by IP$_3$. Alternatively, IP$_4$ may trigger a

FIGURE 5. Schematic Model of IP_3 Receptor Regulation[a]



[a] Inositol trisphosphate (IP_3) binds to a high-affinity binding site on the cytoplasmic face of the IP_3 receptor, which is shown as a membrane-spanning protein containing a channel for passage of calcium out of intracellular stores. Binding of IP_3 to the receptor is inhibited by heparin in a competitive fashion and enhanced at slightly alkaline pH. Inhibition of IP_3 binding by calcium appears to be mediated by a distinct membrane-associated protein. Activation of the cAMP-dependent protein kinase leads to phosphorylation of the receptor protein.

movement of calcium within the cell into IP_3-releasable pools (36). Recently, inositol 1,3,4,5,6-pentakisphosphate (IP_5) has been demonstrated in rat brain and shown to have pharmacological actions suggesting a neurotransmitter role (37).

DAG represents the second "limb" of the phosphoinositide system. Elegant studies by Nishizuka (38) have clarified the biological role of DAG, which involves the activation of protein kinase C. Protein kinase C is a phosphorylating enzyme that is dependent on calcium and phospholipids for its activity and is distinct from protein kinase A, the cAMP-dependent protein kinase. Protein kinase C within the cytoplasm moves to the cell membrane when calcium is elevated within the cell, in part by IP_3-induced release of calcium, or with a rise in DAG, a lipophilic chemical that remains in the cell membrane after its formation from membrane phosphoinositides. DAG activates protein kinase C by enhancing its sensitivity to activation by calcium ions.

Among the numerous proteins that can be phosphorylated by protein kinase C are proteins involved in signal transduction. These substrates include receptors for a wide variety of signaling molecules such as those for acetylcholine, insulin, and epidermal growth factor, transmitter-synthesizing enzymes such as tyrosine hydroxylase, and certain G-proteins such as G_i (38–40).

Protein kinase C exerts prominent feedback effects on several aspects of the phosphoinositide system. It inhibits the ability of transmitters to produce IP_3 (41, 42). In addition, protein kinase C phosphorylates the IP_3 phosphatase enzyme, which degrades IP_3 and thus increases its enzyme activity (43, 44). Protein kinase C even phosphorylates itself, enhancing its sensitivity to calcium, thus producing a feed-forward regulation of its own activity (45).

A direct role for protein kinase C in neurotransmitter actions has been established in various excitable tissues. In our own laboratory, we first showed protein kinase C to regulate cholinergic mechanisms in smooth muscle (46). In the hippocampus, protein kinase C activation blocks a calcium-activated potassium channel, which leads to increased neuronal excitability (47). Protein kinase C also blocks the prominent inhibitory actions of several neurotransmitters, such as serotonin and adenosine (48). The effects of protein kinase C on calcium-activated potassium channels (49) and on adenosine inhibition are also produced by acetylcholine acting through muscarinic receptors. Thus, these effects of acetylcholine presumably involve the phosphoinositide system and protein kinase C.

HETEROGENEOUS LOCALIZATION OF SECOND MESSENGER SYSTEMS IN THE BRAIN

Since the major second messenger systems interact with many of the same neurotransmitters, one would tend to assume that the two systems are ubiquitously distributed throughout the brain. However, although a given second messenger might be present in virtually every cell in the brain, its levels may be orders of magnitude greater in some than in others. Moreover, the existence of multiple subtypes for the various proteins involved in each second messenger system provides other opportunities for regional variations. Molecular cloning techniques have revealed marked biochemical heterogeneity of key components of the phosphoinositide system: seven distinct protein kinase C enzyme subtypes and five of phospholipase C have been identified (50, 51). Differences in their localization, and potential differences in their regulation, may provide yet another means for selective drug action on the phosphoinositide system. Direct investigations have supported the existence of regional specificity and have identified substantial differences in the localizations of components in both the cAMP and phosphoinositide systems.

We localized adenylate cyclase throughout the brain by using ^3H-forskolin, which binds to the enzyme selectively (52). Forskolin binding was localized by autoradiography, a technique in which the radioactive agent bound to thin frozen sections of the brain is visualized. In this technique sections are exposed to photographic emulsion so that development of silver grains occurs wherever the radioactive probe is bound to receptors. We observed striking differences among brain regions. Densities of adenylate cyclase in the caudate and olfactory tubercle were much greater than they were in most other brain areas. In these areas, the adenylate cyclase was contained in the cell bodies of neurons that descend to terminate in the substantia nigra, since lesions of the caudate abolished forskolin binding in the substantia nigra. These cells are recipients of the largest dopamine neuronal input in the brain. Since D_1 dopamine receptors, which are linked to adenylate cyclase activity, are also concentrated in these areas, the high levels of adenylate cyclase in the caudate olfactory tubercle are probably linked to dopamine receptors.

Several different elements of the phosphoinositide system have been localized in the brain. Our first studies visualized protein kinase C throughout the brain by autoradiography using a tritiated phorbol ester. Phorbol esters are chemicals extracted from croton oil that trigger inflammation and promote tumor development in extremely low concentrations (53). Phorbol esters bind to and activate protein kinase C in similarly low concentrations (54–56). We found striking differences in the densities of protein kinase C throughout the brain (52, 57). In addition, the anatomical pattern observed for protein kinase C differs greatly from the localization of adenylate cyclase.

Recent studies revealed differences in the localizations of subtypes of protein kinase C (50). Four of the seven subtypes of protein kinase C have been physically separated and measured in different areas of the brain. mRNAs for three types of protein kinase C have also been visualized by *in situ* hybridization showing differential distribution of the different subtypes among neuronal populations.

At least four distinct forms of phospholipase C have been separated and molecularly cloned (51, 58, 59). We have visualized and localized mRNA for these four enzyme subtypes by *in situ* hybridization, which has revealed strikingly distinct localizations that correlate with specific neurotransmitter receptors (60). For instance, mRNA for the enzyme form designated type A (60) or form I (51) is selectively concentrated in the choroid plexus and the serotonin-containing raphe nuclei, implying a link to serotonin 5-HT-lc receptors (60). This same enzyme subtype is localized to Purkinje cells of the cerebellum, where it presumably mediates the major glutaminergic synaptic input to Purkinje cells from the granule cells (61).

We do not fully understand the functional implications of high levels of adenylate cyclase and phosphoinositide system markers in particular neuronal populations. Nevertheless, by reflecting on the maps of localizations of the two second messenger systems, it might be possible to conceptualize characteristics of brain function that are attributable to one or the other system. For example, since protein kinase C has been implicated in certain forms of synaptic plasticity (i.e., long-term changes in synaptic responses), neurons containing high levels of this pathway may be more versatile in regulating their excitability. Conceivably, insights into the response characteristics of brain systems will be possible by focusing on their repertoire of second messengers.

Within the phosphoinositide system, protein kinase C represents one limb that may be quite distinct from the inositol phosphate component. Therefore, although the activity of phospholipase C on PIP_2 generates both DAG and IP_3, DAG may be formed to a much greater extent from phosphatidylinositol or other phospholipids such as phosphatidylcholine, which occur in very high levels in the brain, than from PIP_2, whose levels are much lower. IP_3, on the other hand, can be derived only from PIP_2. To obtain insight into possible differences in the disposition of the IP_3 and DAG limbs of the phosphoinositide cycle, we localized IP_3 receptors by autoradiography (29, 62).

In general, IP_3 receptors show a similar distribution to that of protein kinase C. For instance, both protein kinase C and IP_3 receptors occur in neurons projecting from the caudate to the substantia nigra and in Purkinje cells of the cerebellum. However, there are some marked regional variations in relative abundance. In the cerebellum, concentrations of protein kinase C and IP_3 receptors are similar. However, in the cerebral cortex and corpus striatum, protein kinase C densities are about 10 times those of IP_3 receptors. Even more dramatic, the substantia gelatinosa of the spinal cord, where sensory afferent fibers terminate, displays an extremely dense band of protein kinase C but is devoid of IP_3 receptors. Similarly, the external plexiform layer of the olfactory bulb, which contains synaptic interactions of incoming olfactory neurons, possesses very high densities of protein kinase C without detectable IP_3 receptors. Accordingly, in these latter two regions it is likely that DAG is formed from phosphatidylinositol with no substantial formation of IP_3 and few IP_3 receptors.

Using antibodies raised against the purified IP_3 receptor protein, we have successfully visualized IP_3 receptors by immunohistochemistry (C. Ross, personal communication). Localization at the light microscopic level reveals essentially the same distributions of IP_3 receptors as were observed by autoradiography with ^3H-IP_3. At the electron microscopic level, IP_3 receptors can be localized intracellularly to a discrete part of the endoplasmic reticulum, confirming earlier studies that this intracellular compartment contains IP_3-sensitive stores of calcium.

LITHIUM: POTENTIAL ACTIONS THROUGH INOSITOL PHOSPHATASES AND G-PROTEINS

Clarifying the therapeutic actions of lithium in psychiatry has proved far more difficult than for many other psychotropic drugs. There are several reasons. Most drugs occur in homologous series of chemical structures that vary in their therapeutic potencies. If a molecular action shows a similar variation, one can feel more confident with a relationship between the biochemical and therapeutic effects. For example, the close correlation between blockade of dopamine D_2 receptors and therapeutic potency in a large series of neuroleptics established a convincing link between dopamine receptor blockade and antipsychotic activity (2, 3). In the case of lithium no such series exists.

Lithium is also intrinsically difficult to understand, since it often relieves both manic and depressive symptoms as well as prevents recurrence of both poles of manic-depressive illness. One can readily conceptualize how a drug such as a neuroleptic can influence receptors for a given neurotransmitter to diminish manic symptoms. Similarly, facilitating the actions of certain biogenic amines may explain antidepressant drug effects. In theory, one might postulate that lithium exerts separate and distinct actions on different neurotransmitter systems to relieve mania or depression. However, abundant clinical evidence suggests that the effects of lithium on the two poles of the illness involve similar mechanisms, since they seem to go hand in hand in individual patients and across patient groups. Indeed, the action of lithium is usually regarded as a "normalizing" effect, preventing excessive excursion away from a euthymic mood level (63).

Actions on a second messenger system might well explain the normalizing effects of lithium on mood. One neurotransmitter system might be hyperactive in mania and another one hyperactive in depression. Through a second messenger system, lithium could block movements of either neurotransmitter system into a hyperactive state. Since second messenger systems are intimately involved in mediating neuronal responsiveness to monoamine and cholinergic systems hypothesized to be involved in affective disorders (64), actions of lithium on the phosphoinositide system and on G-proteins discussed later in this paper may be relevant.

One aspect of the phosphoinositide metabolism not reviewed until now has been the mechanism whereby the phosphate groups are sequentially removed from inositol phosphates (see figure 3). $IP_3(1,4,5)$ is inactivated by a phosphatase that removes the phosphate in position 5. IP_4 is also metabolized by a phosphatase that removes the 5 phosphate. This gives rise to an isomer of IP_3, $IP_3(1,3,4)$, which is different from the active $IP_3(1,4,5)$. The $IP_3(1,3,4)$ has no known biological activity and is thought merely to be a breakdown product. It is metabolized further to isomers of IP_2 that are distinct from that formed from the breakdown of $IP_3(1,4,5)$. All of the various IP_2 isomers are metabolized to corresponding isomers of IP_1, and these in turn are degraded to free inositol. Inositol is then attached to phosphatidic acid to form phosphatidylinositol. Phosphatidylinositol is then sequentially phosphorylated to PIP_2.

A team of investigators at Washington University beginning in 1971 showed that lithium administration to rats depletes brain levels of inositol due to an increase in IP_1 levels, which in turn derives from a selective inhibition of the IP_1 phosphatase (65, 66). With the emergence of the phosphoinositide cycle as a second messenger system, Berridge et al. (67) suggested that lithium's psychoactive effects involve depletion of inositol to slow down the phosphoinositide cycle by preventing the formation of PIP_2 and thereafter IP_3. The extent of "shortfall" of inositol mediators would be proportional to the overall activity of the cycle. One would predict a dampening of synaptic activity associated with the phosphoinositide cycle, particularly for those synaptic systems which are overactive. This formulation would fit nicely with the types of effects needed to explain the normalizing action of lithium.

Studies measuring the biochemical turnover of phosphoinositides and levels of inositol phosphates as a function of lithium treatment have provided evidence that lithium clearly affects inositol phosphate metabolism (68–75). To assess the physiological significance of these observations, we felt it would be important to investigate a synaptic system in the brain directly to determine whether therapeutic concentrations of lithium would influence synaptic activity in the predicted direction.

We took advantage of the system whereby acetylcholine, through muscarinic cholinergic receptors, activates phosphoinositide turnover in slices of the hippocampus (48). In this system, cholinergic agonists that act through the phosphoinositide cycle block synaptic inhibition caused by adenosine. This effect involves protein kinase C because it is mimicked faithfully by phorbol esters.

In this model system, we elicited cholinergic stimulation by applying the cholinergic agonist carbachol and demonstrated that therapeutic concentrations of lithium impair the ability of carbachol to block adenosine (76). The effect of lithium was apparent at 0.5 mM and near maximal at 1 mM of lithium, corresponding to therapeutic concentrations. We observed ionic selectivity, since rubidium had no effect. If lithium were to act by affecting phosphoinositide turnover, this effect should occur before protein kinase C activation. We would predict that lithium should not block the effects of phorbol esters. Indeed, at a time when carbachol effects were abolished by lithium, phorbol esters still reversed the effect of adenosine.

In an earlier study we showed that therapeutic concentrations of lithium influenced neurotransmitter-induced smooth muscle contraction elicited by histamine or cholinergic receptors by acting through the phosphoinositide cycle in smooth muscle (77). This result may also reflect a diminished activation of protein kinase C.

The changes in synaptic transmission we observed with lithium certainly take place through the phosphoinositide system. However, we do not have any direct evidence that inhibition of inositol phosphatases is the mechanism involved. An alternative way in which one could influence the phosphoinositide or other second messenger systems would be through G-proteins. If lithium were to diminish the coupling between G-proteins and receptors, it would also dampen excessive excursion of synaptic transmission involving any transmitter that acts through G-proteins. Avissar et al. (78) have obtained evidence for this type of action. They measured the interactions between receptors and G-proteins in two ways. In one system they measured the ability of carbachol or the β-adrenergic agonist isoproterenol to influence ^{3}H-GTP binding to brain membranes. In another, they monitored the influence of GTP on the competition by muscarinic agonists for radioligand binding to muscarinic cholinergic receptors. In this system, GTP acting through a G-protein decreased the potency of agonists in competing for receptor binding. Using both systems, lithium decreased apparent interactions of neurotransmitter receptors with G-proteins. Similar results were evident in intact rats administered lithium for 12–21 days to produce therapeutic blood levels of 0.6–1.0 mM. These results suggest that lithium interferes with the activity of G-proteins, perhaps by competing with magnesium ions, which are essential for the binding of GTP to G-proteins. Recent studies indicate that lithium's effect on G-proteins may influence phospholipase C activity (79, 80).

These animal studies raise the possibility that effects of lithium on second messenger systems, such as the phosphoinositide system, may contribute to the therapeutic effects of lithium. This suggestion can be tested directly. One could design a series of organic chemical drug-like structures that potently inhibit IP$_1$ phosphatase or phospholipase C. Such agents may have the therapeutic benefits of lithium but without the substantial toxicity that comes from lithium's ionic competition with sodium.

In summary, molecular characterization of second messenger systems has advanced greatly in the last few years. Like the great multiplicity of neurotransmitters and their receptors, second messenger systems, especially the phosphoinositide system, display marked heterogeneity with multiple subtypes of regulatory proteins. It is likely that new psychoactive agents will emerge from the tailoring of molecules for proteins that are key components of these second messenger systems. Studies of the actions of lithium already suggest promising directions.

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Erotomania Revisited: From Kraepelin to *DSM-III-R*

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Erotomania, the persistent delusion of being loved from afar by another person, has defied easy categorization for years. Kraepelin and de Clérambault both discussed the syndrome in detail, but it has recently appeared officially for the first time, in DSM-III-R, *as a subtype of delusional (paranoid) disorder, in a return to the original Kraepelinian formulation. The author reviews the history, theories of etiology, course, and treatment of erotomania. He concludes that the* DSM-III-R *classification is correct and that neuroleptics and enforced separation, although only moderately effective, are the best treatments for troublesome cases.*

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Erotomania is a syndrome whose hallmark is an elaborate, systematized delusion; specifically, the erotomanic patient becomes convinced that she or he is passionately loved by another person (the object), who allegedly uses surreptitious and covert means to signal his or her devotion to the patient. The patients are usually (but not exclusively) women from modest backgrounds, while the objects are generally older men of distinctly higher social and financial status (e.g., executives, physicians, media figures) who are almost inevitably married or unavailable for other reasons. Although the patient insists that the object was the first one to declare his love, and can describe in elaborate detail the evidence for her belief (meaningful glances, messages passed through newspapers or the gestures of passersby, or telepathic communication, for example), in reality patient and object have had at most very casual contact and, in some cases, have never even met. The patient may indignantly reject the imagined love of the object, but more often accepts it and falls obsessively in love herself. Despite vigorous denials of any romantic interest by the startled object, the delusion of being loved persists, usually for years, sometimes requiring hospitalization or legal action to prevent harassment of the hapless victim by the insistent patient.

Erotomania is also known as de Clérambault's syndrome, after the French psychiatrist who meticulously described five cases in 1921 (1). The following account of one of his more dramatic cases, as described by Enoch and Trethowan (2), illustrates many typical features of the syndrome.

Case 1. A 53-year-old Frenchwoman became absolutely convinced that King George V of England was in love with her. She was certain that English sailors and tourists in France were messengers sent by the King to proclaim his love for her. Before having this delusion, she had also believed that an American general and King Edward VII were passionately devoted to her. During several trips to England, starting in 1918, she waited patiently outside the gates of Buckingham Palace; once when she saw a curtain moving in a window, she interpreted this as a signal from the King. She claimed that news of their love was known throughout London, but she also insisted that the King was disrupting her travel plans and that he had arranged for the loss of her luggage, which contained money and portraits of him. Despite these difficulties, which might have been interpreted as attempts to discourage her affections, she persisted in her belief that there was a special relationship between the King and herself, saying, "The King might hate me, but he can never forget. I could never be indifferent to him, nor he to me."

Note the patient's sex, the difference in social standing between the patient and the object, the ideas of reference, and the persistent belief in the object's love despite his imagined strewing of obstacles in the patient's path. This case also illustrates that, although the delusions last for years, in time a new "lover" may replace the old.

For years, erotomania lingered in a kind of diagnostic limbo; some authors considered it to be a unique syndrome, others viewed it as a form of paranoia, and still others saw it as merely a particular manifestation of another underlying condition (e.g., paranoid schizophrenia). In *DSM-III*, for instance, there was no specific mention of erotomania, and a clinician wishing to use a *DSM-III* designation for this condition was forced to use the term "atypical psychosis." Recently, however, erotomania has received the official imprimatur of authority: in *DSM-III-R*, it is listed as a specific subtype of the new diagnostic category delusional (paranoid) disorder, a category that is essentially a return to the original framework of paranoid subtypes

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devised by Kraepelin (3). Because erotomania has now entered the official diagnostic lexicon, the time seems ripe for a review and reconsideration of this controversial condition and its relation to other maladies. In this article we will cover the history of the disorder, theories of its etiology, the course of the illness, and treatment, in an attempt to provide a comprehensive view of this intriguing and often dramatic syndrome.

HISTORY

The idea that love and madness may be related has a long and colorful history; in their excellent chapter on erotomania, Enoch and Trethowan (2) cited cases in the writings of Hippocrates, Plutarch, and Galen. They also cited the work of several seventeenth- and eighteenth-century physicians, who described several pathological variants of love, such as *furor uterinus* (nymphomania), *amor insanus* (erotomania), and erotic melancholy. There was, however, much disagreement about whether passion or mental illness came first in these cases. To add to the confusion, the same terms were often defined differently by different authors. Although some case histories of true erotomania survive from the nineteenth century, no systematic understanding of the syndrome developed until publication of detailed discussions by the great Emil Kraepelin. In *Manic-Depressive Insanity and Paranoia* (3), he brought order out of chaos and drew clear diagnostic boundaries between dementia praecox (schizophrenia), manic-depressive insanity, and paranoia—of which erotomania was considered a subtype.

Kraepelin (3) defined paranoia as "the insidious development of a permanent and unshakable delusional system resulting from internal causes, which is accompanied by perfect preservation of clear and orderly thinking, willing, and acting" (pp. 212–213), that is, without the gross and generalized deterioration typical of schizophrenia. In recent decades, the concept of paranoia has come to be popularly linked exclusively with delusions of persecution, but in fact this is a longstanding distortion of Kraepelin's original schema. Indeed, the delusion of persecution was only one of several subtypes of paranoia that he identified; the others were delusional jealousy and delusions of grandeur.

Kraepelin further subdivided delusions of grandeur into the delusion of 1) being a great inventor, 2) being descended from royalty, 3) being a prophet or saint, and 4) eroticism (erotomania). Kraepelin also considered creating another specific subtype for hypochondriacal delusions; however, he felt that these delusions rarely if ever occurred alone and did not merit a separate category. With this exception, Kraepelin's original formulation of paranoia and its subtypes, now more than 90 years old, is virtually identical to the schema for delusional (paranoid) disorder in *DSM-III-R*; the only other difference is that *DSM-III-R* considers erotomania to be separate from, and not a further subtype of, delusions of grandeur (see table 1).

TABLE 1. Subtypes in Kraepelin's Paranoia and in *DSM-III-R*'s Delusional (Paranoid) Disorder

Kraepelin's Paranoia	*DSM-III-R* Delusional (Paranoid) Disorder
Delusions of persecution	Persecutory type
Delusions of jealousy	Jealous type
Delusions of grandeur	Grandiose type
Eroticism	Erotomanic type
High descent	Somatic type
Inventors	
Prophets and saints	

Kraepelin's description of erotomania was typically concise and elegant. He noted that the patients are usually female and over 30 years old, and that the syndrome progresses from the initial glance that first alerts the patient that she is loved, through the "dreamy hallucinations" that may accompany it, to the inevitable obstacles and disappointments of the affair. As he observes, "the strength of the emotional emphasis of the delusion . . . usually diminishes slowly," but "the essential delusional content remains the same" (p. 251). As with all forms of paranoia, Kraepelin suggested that erotomanic delusions "appear in a certain manner as the morbidly transformed expression of the natural emotions of the human heart" (p. 255), and specifically as "a kind of psychological compensation for the disappointments of life" (p. 259). He scornfully dismissed the Freudian conception of paranoia (i.e., a defense against unacceptable homosexual longings), observing that "these assertions are not supported either by a clearly defined concept of paranoia or by evidence" (p. 265). It is interesting to observe that the Freudian explanation of paranoia has been largely abandoned in recent years, even by the psychoanalytic community (4)—further evidence of Kraepelin's prescience.

Despite Kraepelin's precise (and earlier) description, erotomania has long been linked with the name of Gatian de Clérambault, primarily because of the case descriptions in his 1921 work, "Les Psychoses Passionelles," available now only in the 1942 edition of his *Oeuvre Psychiatrique* (1). 1921 seems to have been a seminal year for the study of erotomania, for it was also then that the English psychiatrist Bernard Hart identified what he called "old maid's insanity," a syndrome identical to erotomania (2). In addition to describing the syndrome, de Clérambault also struggled with the problem of classification, dividing the condition into two categories: the pure cases, in which the delusion develops suddenly and is not accompanied by a generalized psychotic process, and the secondary cases, in which the delusion develops slowly and appears to be only one manifestation of a disorganized, deteriorating course. He felt that his pure cases were distinguished from the paranoid erotic states described by Kraepelin primarily by their sudden onset, and he also emphasized the phenomenon of paradoxical conduct, in which the patient interprets all denials of love by the object, however vigorous, as in fact being secret affirmations of love, tests of the patient's love, or attempts to throw others off the trail of the "lovers." The ingenuity and convoluted reasoning of these explanations can be truly astounding, as his cases demonstrate. De Clérambault also identified common secondary themes of the delusions, e.g., that the object can never be truly happy without the patient's love, that the object's marriage is a sham, or that the patient secretly watches over and protects him.

A careful reading of Kraepelin, however, suggests that de Clérambault's rationale for distinguishing the pure form of his *psychose passionelle* from Kraepelin's erotomania—on the basis of sudden onset—is faulty. Although Kraepelin felt that the details of the erotic delusional system accumulate slowly, he was well aware that the patient can trace her awareness of being loved to a single, specific incident, which by itself is sufficient to convince her of the object's love (3). Furthermore, he too described paradoxical conduct and how the patient explains it away. Finally, he was quite clear in stating that intellectual functions are preserved in erotomania, that the delusions and ideas of reference are restricted to the idea of being loved, that the patient insists that the object was the first to fall in love, that there are no prominent hallucinations, and that there is no widespread psychotic process resembling schizophrenia. These are essentially the characteristics of de Clérambault's pure cases, and there seems to be no justification for distinguishing between them. On the other hand, both Kraepelin and de Clérambault were correct in noting that sometimes erotomanic delusions can occur incidentally as part of a more generalized psychosis, most commonly in paranoid schizophrenia.

In more recent years, in fact, most of the controversy surrounding erotomania has been focused on whether it *ever* exists as an entity separate from schizophrenia. Pearce (5) felt that the syndrome was bona fide, and Raskin and Sullivan (6) described two cases and felt that they were different from schizophrenia. Hollender and Callahan (7) also believed that nonschizophrenic cases did exist and should be considered paranoid subtypes. Seeman (8) described eight cases, separating them into two groups, one with fixed and more severe delusions and the other with recurrent and less bizarre erotic delusions; at least three members of her group with recurrent delusions were clearly not schizophrenic, and even the members of her group with fixed delusions appeared to meet criteria for delusional but not necessarily schizophrenic disorders. Rudden et al. (9) felt that their 1980 case fit well into Seeman's recurrent category. Taylor et al. (10), in one of the relatively few studies of erotomania in men, concluded that three of their four patients had true erotomania without schizophrenia. Munro et al. (11) reported two pure cases and agreed that the syndrome was a subtype of paranoia; Munro's 1986 prediction (12) that *DSM-III-R* would recognize it as such proved to be correct.

By contrast, several other authors have claimed that erotomania always exists merely as a particular symptom of schizophrenia or another disorder. Ellis and Mellsop (13) reviewed 58 published cases, found that only two of them met all the criteria proposed by de Clérambault for pure cases, and proposed that the category be discarded. Similarly, Sims and White (14) and Hayes and O'Shea (15) concluded that cases of erotomania could best be thought of as cases of schizophrenia.

The claims of these authors notwithstanding, it seems clear from a review of the published record that there are indeed a number of cases, some of which have been cited here, that fit Kraepelin's and/or de Clérambault's descriptions of erotomania without evidence of schizophrenia or other conditions. Furthermore, the differences between Kraepelin's and de Clérambault's descriptions are vastly outweighed by their similarities, and the specific characteristics of the syndrome, as discussed by either author, fit well into Kraepelin's broader conception of paranoia—now called delusional (paranoid) disorder. Thus, I conclude that the authors of *DSM-III-R* are correct in identifying and confirming an erotomanic subtype of delusional disorder, in what appears to be a posthumous and long overdue diagnostic triumph for Kraepelin.

THEORIES OF ETIOLOGY

True to custom, the authors of *DSM-III-R* refrained from offering a causal explanation for erotomania; they are perhaps the only ones to resist this temptation, since other scholars of the subject, demonstrating considerably less self-control, have proposed a multitude of theories. Historically, the fact that the syndrome most often occurs in "individuals of defective sexual life, not much inclined to copulation, sometimes in old maids who have never had an opportunity of marrying" (2, p. 21) has not escaped notice, suggesting extreme sexual frustration as the cause. We have already heard Kraepelin's rather sympathetic explanation ("a compensation for the disappointments of life") and his rejection of the Freudian approach. De Clérambault suggested that *orgeuil sexuelle* (sexual pride) is at the root of the condition; the implication is that, stimulated by a lack of real (sexual) approval, erotomanic delusions develop as a means of satisfying the inherent demands of pride. Translated into modern terminology, one might say that the delusions provide narcissistic gratification when life cruelly fails to do so. This formulation reveals the essential convergence of Kraepelin's and de Clérambault's thought, however strongly de Clérambault may have emphasized the differences.

Hollender and Callahan (7), noting the physical unattractiveness of their patients, and Raskin and Sullivan (6), whose two patients had recently lost their husbands, concurred with the preceding interpretation. Seeman (8), by contrast, proposed different causes for the erotomania found in her two patient groups; for the more disturbed group with fixed delusions, she suggested that the delusions serve as a defense against heterosexual urges (since the patients unconsciously know that there is no danger of true sexual activity occurring), aggression, and low self-esteem. For the better-functioning patients with recurrent delusions, she hearkened back to the Freudian notion of erotomania as a defense against homosexual wishes, coupled with "an attempt to incorporate power and success into one's own self-image."

Enoch and Trethowan (2) reviewed many of the proposed causes and, although they did not defend a particular thesis, placed most emphasis on the narcissistic argument. Taylor et al. (10) noted that, in contrast to traditional psychoanalytic predictions, all four of their male patients had heterosexual, not homosexual, fantasies or experiences. These authors were more impressed by the patients' lonely, isolated lives and their extreme dependence on their parents. Evans et al. (16), discussing a single case in detail, proposed that the erotomanic delusions were a form of pathological mourning. They admitted, however, that their speculations on the dynamics of the patient were not confirmed by the treatment process.

Clearly, there is no broad agreement on a single psychodynamic explanation for erotomania. Various authors have invoked heterosexuality, homosexuality, narcissism, and other major dynamic themes as possible sources of the delusions. There are several reasons for this. In the first place, there are relatively few published cases (although in practice the syndrome is more common than generally appreciated), making it difficult to confirm a consistent pattern, even if one existed. More importantly, few of the published accounts suggest that the authors had truly detailed knowledge of the patients' inner lives, leaving any causal theory more speculative than substantiated. It thus seems most likely that the authors' preexisting allegiances to various psychodynamic theories have had more influence on their proposed explanations than did information from the patients. This phenomenon is not unique to the study of erotomania; nevertheless, it is an obstacle to progress. Finally, of course, there may well be several dynamic, or even biological, factors involved, making it impossible to discover a single cause that is primary in every case.

Certain patient characteristics recur, nevertheless, and this may prove helpful in deciding which of the various theories are most plausible. The most striking observation is that the typical patient, whether male or female, leads a withdrawn, socially empty, and presumably lonely life; few are married, many have no sexual contacts for years at a time, most labor in subordinate or menial jobs, and some are notably unattractive. By contrast, the objects are always, in reality or in fantasy, of superior intelligence, status, looks, authority, or some combination thereof, and, by definition, the patient feels herself to have been plucked from her obscurity and singled out for the object's love. Although other factors may well be involved in specific cases, this strongly supports the notion that erotomanic delusions serve narcissistic needs, perhaps expressed as the delusion of being loved because that is the ultimate form of approval. Even if, as in the following case from my own practice, the patient chooses to reject the advances of her "lover," at least they have been passionately offered (or so she imagines), posing a stark contrast to the otherwise bleak emotional landscape of her life.

Case 2. Ms. B, a 65-year-old retired clerk, was admitted for psychiatric treatment following her attack on an elderly bank manager who lived in her apartment building. She claimed that although he had never spoken to her out loud, he had been contacting her telepathically for months with romantic messages; she "hinted" that these messages contained sexual overtones. She said that she could tell he was interested in her by the way he looked at her. After she accosted him several times to protest, he denied any interest in her and obtained a restraining order barring any contact between them. Unable to restrain her indignation, she followed him to his office, leaped at him across his desk, and allegedly tried to strangle him. Later, however, she admitted only to having touched his tie—perhaps displaying, to use a Freudian phrase, displacement from below.

Ms. B looked and acted like the stereotypical image of a spinster; she dressed primly, had a modest, old-fashioned demeanor, and had labored in obscurity at the same job for many years until, she explained, she was forced out of the job during an office reorganization. (I later found out that a previous erotomanic episode with the head of the company was actually responsible for her early retirement.) She had never married, lived alone, and rarely socialized, even with family members. She apparently had had only one sexual experience, an unhappy one at that, as a young woman, and had lived chastely ever since. She was fully oriented, showed no sign of affective illness, and had no other delusions save those concerning the bank manager.

Treatment with neuroleptics stemmed the tide of unwanted messages but had no effect on her firm belief in the man's interest in her or on her feelings that she had been treated unfairly by the legal system. During the one appointment she kept with me after her discharge from the hospital, she announced with glee that she had stopped taking her medication, despite my warning of the dire consequences to follow. She then left the office and was never heard from again; my attempts to contact her were fruitless.

The preceding case history, emphasizing the role of narcissistic needs, raises several questions. First, if erotomania truly is a subtype of delusional disorder, and if the theory of narcissistic needs is correct, might it also apply to other, nonerotomanic delusional subtypes (e.g., delusions of persecution), or should we look to a common defense mechanism (e.g., projection) rather than a common underlying need, as a way of linking the various delusional subtypes? Are the lives of other delusional patients as notably empty and undistinguished as those of erotomanic patients? Finally, what factors determine whether an erotomanic delusion develops in the lives of two different but equally obscure individuals? Answers to these questions might advance the debate about the dynamic underpinnings of the syndrome.

COURSE OF THE ILLNESS

In contrast to the debates over the true nature of the syndrome and its underlying causes, there is near unanimity of opinion as to its course. Kraepelin, de Clérambault, and nearly all modern authors have emphasized the extreme persistence of the erotic delusions (albeit sometimes with reduced intensity) despite all protestations by the bewildered object or attempts by medical or legal authorities to dissuade the patient. Ms. B is a case in point. Kraepelin believed that "the natural issue of paranoia is probably, as a rule, a residual delusion" (3, p. 251). De Clérambault (1) described a case in which the delusion lasted 37 years; Enoch and Trethowan's four cases all lasted at least several years (2). Hollender and Callahan (7) published cases of 15 years' duration, Seeman (8) described cases of 10 years' duration, and other modern authors (6, 10, 17) have published numerous cases of erotic delusions lasting at least several years. The strength of the delusions may wax and wane (3, 10), the barrage of letters and phone calls to the object may diminish, and the patient may regretfully learn to live with the unconsummated nature of the "love affair," but there is nearly always some remnant of the delusion, and most patients continue to insist for years that they are loved from afar.

Although this is the typical pattern, it is not absolutely universal; there are rare reports of cases resolving after direct confrontation with the facts (4, 9), but generally this tactic is completely useless. In addition, there are numerous instances in which the patient gradually abandons her longstanding delusion, only to fixate on a different object months or years later (1, 10). Five of Seeman's eight patients, the patients with recurrent delusions, had repeated, relatively brief delusions involving different men each time (8); however, the unusual brevity of each episode (several months) sets them apart from most other case reports. *DSM-III-R* allows for chronic, waxing and waning, or recurrent courses, as well as briefer, nonrecurring episodes.

TREATMENT

Finally, we come to the vexing problem of treatment, and here, alas, there is much room for improvement. Of the medical treatments available, neuroleptics are the most useful, although, as with other circumscribed delusions, their effect is usually modest, leaving the core delusion untouched. When they work, they serve primarily to reduce the intensity of the delusion and the ideas of reference that accompany it (7, 9–11, 18). Occasionally, ECT has been used as a treatment, but it only rarely produces a marked improvement (17) and sometimes leads to only moderate change (11). There is no evidence that individual psychotherapy helps these patients; the few reports of patients in regular treatment (8, 17) are not encouraging, and anyone who has personally tried to shake the foundation of a fixed delusion can easily imagine the frustration inherent in this method. Some patients (Ms. B, for example) need to be forcibly separated from their objects, at least temporarily, by hospitalization, restraining orders, or, occasionally, jail (if they commit criminal offenses related to their delusions). Men in particular seem to be more aggressive in their pursuit of love, and although they make up only a minority of the total cases of erotomania (perhaps 20%–30%), they are overrepresented in the forensic population (10). Some authors feel that forced separations are at least as effective at diminishing the delusions as are any medical treatments (10).

Unfortunately, the overall prognosis for erotomanic patients is rather gloomy, and the lives of their delusionary objects may be disrupted for years by harassment and, in extreme cases, by violence. Imprisonment aside, the best that unlucky victims can hope for in such cases is that fear of punishment will persuade patients to keep their delusions to themselves or that, in time, their attentions will shift to another imagined lover. Seen in another light, however, perhaps erotomania, if kept under control, is not an altogether negative phenomenon, since it may provide solace for a few lonely souls, who might otherwise spend their lives in unrelieved isolation and solitude.

CONCLUSIONS

Based on the preceding review, my conclusions are as follows. 1) There is a specific syndrome of erotomanic delusion without schizophrenia, occurring predominantly, although not exclusively, in women. 2) The new *DSM-III-R* category of delusional (paranoid) disorder, which is virtually identical to the original Kraepelinian formulation of paranoia, properly includes erotomania as a separate subtype. 3) The erotomanic syndromes described by Kraepelin and de Clérambault are identical clinically, and there is no reason to distinguish between them. 4) The psychodynamic origin of erotomania is probably related to unmet narcissistic needs. 5) The delusions are persistent but may diminish in intensity and may shift to a new object. 6) Neuroleptics and enforced separation from the object, although admittedly imperfect, are the best treatment options currently available.

There is no question that new cases of erotomania will surface, and only by studying them carefully will we learn more about the condition, especially about underlying causes and, perhaps, about better treatment. However, by returning to Kraepelin's diagnostic schema, now nearly 100 years old, *DSM-III-R* has, paradoxically, taken a major step forward toward a modern understanding of this fascinating syndrome.

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Simple Schizophrenia: Past, Present, and Future

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The diagnostic category called simple schizophrenia has disappeared from official American nosology but has been retained in ICD-9. *The diagnosis has a long history, was one of the traditional schizophrenic subtypes identified by Bleuler, and was later accepted by Kraepelin. The authors provide a historical overview of the concept, review its modern successors, and provide recommendations for its inclusion in* DSM-IV *as a proposed diagnostic category needing further study.*

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In use for nearly 70 years, the diagnostic category of simple schizophrenia was unceremoniously deleted from *DSM-III*. Concommitantly, a new diagnosis—schizotypal personality—was created and, together with a redefined schizoid personality category, was believed to provide an adequate substitute for simple schizophrenia. In this article we trace the origins of simple schizophrenia, review its history, and consider the reasons for its demise. Further, we address whether its demise was justified, what its modern successors are, and whether it should have some role in the future.

ORIGINS OF SIMPLE SCHIZOPHRENIA

The concept of simple schizophrenia dates to the turn of the century, during a time when the concept of schizophrenia was in great ferment. In 1896, in the fifth edition of his *Textbook of Psychiatry*, Emil Kraepelin brought together the formerly disparate concepts of hebephrenia, catatonia, and paranoia into a single entity that he called "dementia praecox." The name of this new disorder reflected his belief that its pathognomonic feature was mental deterioration, usually occurring in young persons. Eugen Bleuler, however, felt that the process in the disorders described by Kraepelin represented a splitting of psychic functions, and in 1908 he renamed the disorder "schizophrenia," which he thought was a more appropriate term than "dementia praecox" (1). He expanded Kraepelin's narrow concept of dementia praecox on the grounds that the condition of patients did not always deteriorate, nor did the disorder always appear in adolescence. Furthermore, Bleuler felt that a group of schizophrenias, rather than one disease process, existed. He acknowledged Kraepelin's three subtypes (hebephrenia, catatonia, and paranoia) but included two new ones. These subtypes were schizophrenia simplex, a simple type of schizophrenia characterized by social withdrawal and affective flattening but not by prominent catatonic, hebephrenic, or paranoid features, and latent schizophrenia, which was even more vaguely defined. Bleuler believed that latent schizophrenia was probably very common and implied that the diagnosis should be used for odd or eccentric persons who arouse "the suspicion of schizophrenia" (1, p. 239). Simple schizophrenia was later accepted by Kraepelin and included in the eighth edition of his *Textbook of Psychiatry* (2).

Credit for initially describing simple schizophrenia is usually accorded to Bleuler in 1911. However, the essential features of the disorder were described much earlier. Bleuler himself (1) traced the syndrome to Karl Kahlbaum (3) who in 1890 separated heboidophrenia from hebephrenia, which Ewald Hecker (4) had delimited in 1871. Heboidophrenia, wrote Bleuler (1), was "no more than a milder form of hebephrenia manifesting itself chiefly by changes in character" (p. 6), including only disturbances of social feeling, tact, and behavior.

Bleuler also identified simple primary dementia as a forerunner of simple schizophrenia and credited Arnold Pick (in 1891) and Robert Sommer (in 1894) with its description (1, p. 6). However, the condition was identified earlier by Thomas Clouston as "primary dementia." Bleuler cited an 1888 address by Clouston: "The patients became less acute in emotion and judgement, less powerful in volition, less able to do their work or take care of themselves, and less social and more 'silly,' these symptoms gradually going on to marked dementia" (5, p. 335).

It was Otto Diem (6), however, who in 1903 published the monograph "Die einfach demente Form der Dementia Praecox (Dementia simplex)" ["The Simple Dementing Form of Dementia Praecox"] and probably

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deserves credit for the earliest formulation of simple schizophrenia. The syndrome described by Diem was similar to the later and better known description by Bleuler. Diem wrote:

> We can summarize thus: In addition to the clinical pictures of hebephrenia, catatonia, dementia paranoides and the paranoid form, which all terminate in the particular dementia of dementia praecox (after Kraepelin), there is a further type of clinical course leading to the same terminal state—to the same disturbance of intelligence and affect. But here the onset is regularly simple, indolent, without special prodrome, and the sickness develops without acute episodes and remissions, without marked manic or melancholic dejectedness, without illusions or hallucinations, and without the other particularities of the above mentioned forms characteristic of dementia praecox: catalepsy, tics, affectations, mannerisms, stereotypies, negativism, mutism, etc. (6, pp. 185–186)

As Diem had divided the symptoms of schizophrenia, Bleuler, too, described both the essential and the accessory symptoms of the disorder. The essential symptoms consisted of those now known as Bleuler's four A's: autism, ambivalence, associative loosening, and affective disturbances. He suggested that these elements were fundamental and universal in schizophrenia. This formulation led him to divide the phenomena that these patients experience into essential and accessory symptoms. According to Bleuler (1), schizophrenia could be identified by the presence of essential symptoms alone, while the accessory symptoms were felt to be less important and were not found in either the simple or the latent subtypes. These accessory symptoms consisted of psychotic features, such as hallucinations and delusions, catatonia, somatization, changes in speech and writing, and certain mnestic disturbances. According to Bleuler, the course of simple schizophrenia showed weakening of affect and intellect and a decreasing capacity for self-care and work. Further, the disorder led, he believed, to the mental deterioration seen in other subtypes of schizophrenia. Bleuler (1) wrote:

> This group is rarely found in hospitals, but outside it is as common as any of the other forms [of schizophrenia]. In private practice we often see it, indeed as frequently in the relatives who bring the patients as in the patients themselves. On the lower levels of society, the simple schizophrenics vegetate as day laborers, peddlers, even as servants. They are also vagabonds and hoboes as are other types of schizophrenics of mild grade. On the higher levels of society, the most common type is the wife (in a very unhappy role, we can say) who is unbearable, constantly scolding, nagging, always making demands but never recognizing duties . . . . Furthermore, there are many simple schizophrenics among eccentric people of every sort who stand out as world saviors and reformers, philosophers, writers and artists, beside the "degenerated" and deteriorated. (p. 236)

Kraepelin (2) later embraced the concept of simple schizophrenia. He wrote:

> Dementia simplex consists of an impoverishment and devastation of the whole psychic life which is accomplished quite inperceptibly . . . . The former good, perhaps distinguished, scholar fails always more conspicuously in tasks which til then he could carry out quite easily, and he is more and more outstripped by his companions. He appears absentminded, thoughtless, makes incomprehensible mistakes . . . . Others become idle and indifferent, stare for hours at their book without reading, give themselves no trouble with their tasks, and are not incited either by kindness or severity. (pp 90–91)

Kraepelin (2) also described certain affective changes in simple schizophrenia:

> The patients become timid, lachrymose, or impertinent, irritable, malicious . . . . Their circle of interests becomes narrower; their relations to their companions became cold; they show neither attachment nor sympathy . . . . Ambition and pleasure in the usual occupation become extinct, work and plans for the future are silent; inclination and ability for useful occupations disappear . . . . A considerable number in the end fall into the crowd of beggars and vagabonds, and oscillate hither and thither in a half-witted state from year's end to year's end between public highway and workhouse, wherever anew the hopeless attempt is made to turn them around. (pp 91–92)

Kraepelin (2) also believed, along with Bleuler, that the disorder led to mental deterioration—hence dementia, although he stated clearly that the dementia was not profound (p. 93).

SIMPLE SCHIZOPHRENIA AFTER BLEULER

As a result of the contributions of Diem, Bleuler, and Kraepelin, simple schizophrenia became established as a psychiatric entity and was incorporated widely into textbooks and classification systems. The rapid acceptance of simple schizophrenia is illustrated by its inclusion in influential textbooks of psychiatry that were published over the ensuing decades. Representative of textbook descriptions are those by White (7), Henderson and Gillespie (8), Noyes (9), Sadler (10), Mayer-Gross et al.(11), Lehmann (12), and Day and Semrad (13). These descriptions uniformly included simple schizophrenia among the traditional subtypes of schizophrenia. Although their accounts borrowed heavily from Bleuler and Kraepelin, they provided little new information about the syndrome and often reported contradictory data.

A review of the definitions in these seven textbooks, spanning almost 60 years, shows that of eight symptom complexes, only two—avolition and deteriorating course—were accepted in all the texts as part of the simple schizophrenia syndrome. Two sources (8, 10) suggested that thought disorder may occur, but the others did not. White (7) and Sadler (10) included motor signs (bizarre mannerisms and negativism), which were not accepted by Bleuler or Kraepelin. White (7), Henderson and Gillespie (8), Noyes (9), and Sadler

(10) included changes in mood, but the other authors either were equivocal or did not address this symptom. Bleuler and Kraepelin believed that the disorder led to mental deterioration, yet only Sadler (10) agreed; Henderson and Gillespie (8) did not (i.e., "memory is retained"), and the other authors made no comment. These varied descriptions of simple schizophrenia also included other symptoms. White (7) and Sadler (10) noted listlessness, inattention, poor concentration, and lack of insight; Lehmann (12) and Day and Semrad (13) listed sleep/wake cycle disturbances. All authors noted insidious onset, usually in adolescence, and shallow or blunted affect. Clearly, the multiple competing definitions offered in the textbooks contributed to the ever-widening boundaries encompassed by simple schizophrenia.

Simple schizophrenia eventually found its way into the sixth revision of the *International Classification of Diseases* (*ICD-6*) in 1948, *DSM-I* in 1952, and *DSM-II* in 1968. In *DSM-I*, simple schizophrenia was described as a type of reaction characterized by a "reduction in external attachments and interests and by impoverishment of human relationships." It was felt to involve an adjustment on a "lower psychobiological level of functioning, usually accompanied by apathy and indifference but rarely by conspicuous delusions or hallucinations." The concept of mental deterioration was included, but not dementia. In *DSM-II*, the definition of simple schizophrenia was relatively unchanged from that in *DSM-I*, although the deterioration process was emphasized. The syndrome was described as a psychosis "characterized chiefly by a slow and insidious reduction of external attachments and interests and by apathy and indifference leading to impoverishment of interpersonal relations, mental deterioration, and adjustment on a lower level of functioning." The condition was described as "less dramatically psychotic" than the other subtypes of schizophrenia. The definition in the ninth and most recent edition of *ICD* is similar and includes the notions of deterioration, social impoverishment, and avolition but not mental decline. Further, *ICD-9* cautions that the diagnosis should be made "sparingly, if at all."

Simple schizophrenia continued to expand, with the official definitions later including the possibility of hallucinations and delusions. These official definitions, along with the textbook descriptions, described a disorder with indistinct boundaries, unclear symptoms, and, as a result, doubtful validity.

CRITICISM OF THE SYNDROME

Despite its wide acceptance and its inclusion in diagnostic systems, simple schizophrenia came under early criticism. In a 1936 bibliography Lewis (14) noted:

> In many clinics using the classification of Kraepelin . . . the group known as "simple praecox" is a very heterogeneous affair. It serves the praecox group as a sort of diagnostic waste basket into which every undifferentiated problem is neglected, serving as the term "neurasthenia" did in the days before Freud gave us some leads for differentiation. Therefore, in the "simple praecox" group one finds borderline cases of feeblemindedness, deteriorated hebephrenia, psychopathic personalities, peculiar character fixation, etc., classed together. (p. 32)

Lewis took a dim view of research on this syndrome, noting that any such research would "mean nothing" because of its heterogeneity.

In a more thorough and highly critical review, Stone et al. (15) noted that 1) between 1930 and 1968 only one significant clinical paper (16) was produced; 2) the diagnosis was rarely used (0.04–0.24% of a state hospital population were given the diagnosis, although these patients probably would not be found in great numbers in state hospitals); 3) the existing criteria were vague or contradictory and failed to distinguish between the essential and accessory symptoms described by Bleuler; and 4) there was no agreement among authors on whether thought disorder was present. Stone et al. criticized the wholesale acceptance of simple schizophrenia despite the paucity of supporting clinical evidence and the acknowledgement by experts such as Lewis (14) that it was an ill-defined concept. On the basis of a review of eight cases of persons diagnosed as having simple schizophrenia, these authors reported that other existing diagnostic categories, such as severe personality disorders or chronic schizophrenia, were probably more appropriate. Stone et al. observed that even Kant's (16) findings were at variance with the classical descriptions of simple schizophrenia, and although Kant did not interpret them that way, the findings failed to support the existence of the syndrome. Kant (16) surveyed a state hospital population and found that 81, or 5.1%, of the schizophrenic population had simple schizophrenia. When he examined 64 of the 81 patients with simple schizophrenia, only two had no evidence of hallucinations or delusions, either historically or on current mental status examination. In 43% of the subjects, psychotic symptoms were pronounced. Stone et al. (15) believed, and Kant's (16) data would indicate, that in many cases of simple schizophrenia, the presumed lack of delusions or hallucinations is based on inadequate information. White (17) stated the situation this way: "The more carefully the history is taken, the less great are the chances that the case will be classified under the simple form. This is because the patient may have experienced delusions and hallucinations, and may have engaged in queer behavior when by himself, without revealing these facts to anyone." On the basis of the information they reviewed, Stone et al. (15) recommended that the diagnosis be discarded.

The descriptive validity of the syndrome also came under fire. Data collected in the International Pilot Study of Schizophrenia (18) failed to substantiate the usefulness of the classic subtypes of schizophrenia, including the simple subtype. It was noted that patients with simple schizophrenia had quite low ratings of psychotic symptoms, but this trend would be expected. Strauss and Carpenter (19), who assisted in the project, observed that the traditional subtypes were of limited usefulness, and distinctions were less apparent among patients than among textbook descriptions. They concluded that the simple and latent subtypes, in the absence of psychotic features, should be considered as outside the realm of schizophrenia. They cautioned, however, that "this does not deny the possibility of a subpsychotic or even subclinical schizophrenia, but we cannot presently identify such cases reliably" (p.38).

Other data also cast doubt on the validity of the simple schizophrenia diagnosis. Helmchen (20) compared the phenomenology of all 10 *ICD-8* schizophrenic subtypes. No symptom appeared with any special frequency in simple schizophrenia, suggesting that the diagnosis was used for persons whose symptoms were indistinct or uncertain. Helmchen observed that the "differential diagnosis between simple schizophrenia and schizoid personality is often impossible, unless the course is considered."

DSM-III

DSM-III, published in 1980, represented a major advance in psychiatric classification, at once both praised and condemned for introducing operational criteria to help standardize psychiatric diagnosis. The American Psychiatric Association's Task Force on Nomenclature and Statistics, responsible for developing *DSM-III*, felt that one of the first problems for the new manual was to set the boundaries of schizophrenia (21, 22). The committee members noted that the concept of schizophrenia was very broad and explicitly included two nonpsychotic forms, simple and latent schizophrenia. In order to narrow the concept of schizophrenia, it was decided to restrict the disorder to an illness in which at some time there had been characteristic delusions, hallucinations, or marked formal thought disorder.

The new conceptualization of schizophrenia had resulted from a climate of change begun years earlier. The broad, Bleulerian concept of schizophrenia, which emphasized psychological aspects of the syndrome, was predominant in the United States through the late 1960s and into the early 1970s. The narrower, Kraepelinian approach, stressing phenomenology and course, was prominent among British and Continental psychiatrists, however. This situation led to great differences in the prevalence of diagnosed schizophrenic and manic-depressive illness here and abroad. In New York hospitalized psychiatric patients were more likely to be diagnosed as schizophrenic than manic-depressive, whereas the reverse was true in London. These differences were uncovered in the United States/United Kingdom diagnostic project (23) and confirmed in the International Pilot Study of Schizophrenia (18). In the latter study, schizophrenia in nine countries was compared. The major finding was that similar criteria were used in seven countries, but broader criteria were used in the United States and the Soviet Union. In the context of these studies, an interest in reliable diagnosis emerged. Bleulerian symptoms, with their breadth and imprecision, did not lend themselves to close agreement among clinicians. On the other hand, hallucinations and delusions as defining features are clearly discordant with normality and are easier to identify reliably. These forces led to the reshaping of the American concept of schizophrenia into that of a relatively severe psychotic disorder, bringing it closer to the original ideas of Kraepelin and more in line with European practice. Along with the changing conceptualization of schizophrenia and growing criticisms specific to simple schizophrenia, the formerly wide diagnostic net of schizophrenia was narrowed, and the simple and latent subtypes were deleted from *DSM-III*.

The new definition adopted for schizophrenia was derived from both the St. Louis criteria (24) and the Catego system developed by Wing for the International Pilot Study of Schizophrenia (18); it emphasized a long duration of illness and the presence of florid psychosis. Specifically, the new criteria required 1) a period of active psychotic symptoms such as hallucinations, delusions, or certain disturbances in form of thought and 2) a duration of disturbance or impairment of at least 6 months. The rationale for restricting the diagnosis was to identify a more homogeneous population with regard to early onset, greater prevalence in family members, severe impairment, and differential response to somatic treatment. Because simple and latent schizophrenia, by definition, were not accompanied by these abnormalities, they could not be considered forms of schizophrenia within the narrow limits established in *DSM-III* (25). Thus, these categories were eliminated because of the difficulty in differentiating them from severe personality disorders and the lack of evidence that patients with simple or latent schizophrenia share important features with the other traditional subtypes. The task force members felt that patients who had not been frankly psychotic and who were formerly diagnosed as having latent or simple schizophrenia would probably fit into a newly created category—either schizotypal or borderline personality—or the redefined category of schizoid personality (25).

Although simple schizophrenia is no longer included in American classification schemes, the diagnosis is still included as a schizophrenic subtype in *ICD-9* and is used in other countries.

SUCCESSORS TO SIMPLE SCHIZOPHRENIA

Among the newly created diagnoses was schizotypal personality. The definition of this disorder was developed largely on the basis of data from the Danish adoption study of Kety et al. (26), which suggested that relatives of schizophrenic patients had mild forms of the disorder. The criteria used by the task force members (27) to define schizotypal personality were based on the experience of Kety et al. These criteria included magical thinking, ideas of reference, odd speech, unusual perceptual experiences, eccentric behavior, inadequate rapport, suspiciousness or paranoid ideation, and undue social anxiety. In their study, Kety et al. derived these criteria from case records of adopted offspring of schizophrenic patients and control subjects who were considered to have characteristics related to schizophrenia. These characteristics were more frequent in the biologic relatives of the schizophrenic probands than in their adopted relatives or the biologic relatives of the control subjects. The term "schizotypal," however, was derived from Rado's (28) "schizotype," a term which he applied to patients who may or may not have been overtly psychotic but who manifested "schizotypal organization," his term for a collection of psychodynamic traits. Meehl (29) refined and elaborated a similar formulation and, like Rado, advocated the term "schizotype" for the personality organization observed in persons with a genetic predisposition to schizophrenia.

Whereas the schizotypal personality category had been created to identify the eccentric character of genetic relatedness to schizophrenia, other "borderline" conditions, long of interest to psychoanalysts, were placed in another new category, borderline personality. This new category represented an attempt to identify persons with enduring personality features characterized by instability in sense of identity, interpersonal relationships, impulse control, and mood. Thus formulation incorporated the ideas of Zilboorg (30), Hoch and Polatin (31), Frosch (32), Kernberg (33), and others and was supported by a factor analytic study (27) of the symptoms of a group of more than 800 patients diagnosed as borderline. Thus, the delimitation of these two new personality disorders arose from an attempt to differentiate, within the context of *DSM-III*, the chronic instability of borderline personality, in which regression was said to be accompanied by loss of reality testing, from borderline schizophrenia, in which psychotic-like symptoms were presumed to be due to a genetic relationship to schizophrenia.

While the schizotypal and borderline personality categories were created by task force members to fill theoretical vacuums, schizoid personality was merely redefined. The term "schizoid" had originally been used to describe the isolation and emotional distancing that occurred in patients with schizophrenia before its onset and during remissions, as well as in schizophrenic patients' relatives. Kraepelin (2) had noted that in retrospect, children who became schizophrenic were particularly "quiet, shy, reserved." Bleuler had conceived of the schizoid element as a dimension of all personalities, with schizophrenia as its extreme prototype. For him, the line between the normal person with a schizoid component and the schizoid nature of schizophrenia was not clear. He also referred to the schizoid characters in families of schizophrenic patients as "people who are shut-in, suspicious, incapable of discussion, people who are comfortably dull" (34, p. 441). Thus, the term "schizoid" evolved in the context of an attempt to understand the nature and genetic basis of schizophrenia.

Eventually, the concept of schizoid personality was embraced by dynamically oriented clinicians who broadened the concept to encompass those persons who had difficulty with intimacy and, later, to describe a wide range of behavioral peculiarities (35). In *DSM-I* the disorder was defined as an inherent trait characterized by avoidance of close relations with others, inability to express hostility or even ordinary aggressive feelings directly, and autistic thinking. Persons with these qualities were described as aloof, emotionally detached, fearful, avoiding competition, and often eccentric. In *DSM-II* the description was relatively unchanged. Although the descriptions in *DSM-I* and *DSM-II* of both simple schizophrenia and schizoid personality appeared to dovetail, these manuals took care to note that schizoid personality is not accompanied by deterioration of functioning, unlike simple schizophrenia.

In the process of developing *DSM-III*, the committee members noted that the schizoid personality disorder category would be best served by restoring the original intent of the diagnosis; in doing so they divided the *DSM-II* schizoid personality category into three separate clusters corresponding to three personality disorders: schizotypal, schizoid, and avoidant (25). Persons with eccentricities were felt to be best described by *DSM-III* schizotypal personality disorder. The distinction between schizoid and avoidant personalities was based on whether there was a defect in the motivation and capacity for emotional involvement (schizoid) or avoidance of desired close relationships because of fear of rejection (avoidant). These descriptive distinctions, as yet unproven, were believed to have therapeutic and prognostic significance.

It was assumed that all persons with *DSM-II* simple schizophrenia would fit into one of the newly created or redefined *DSM-III* categories. There was some debate, however, during the revision of *DSM-III* (R. Spitzer, personal communication, May 1988) about whether a diagnosis for a simple deteriorated state should be reintroduced to describe nonpsychotic persons with avolition, apathy, and a markedly deteriorating course. These negative or defect symptoms had been incorporated into early definitions of simple schizophrenia, but they were not traditionally included as core features of personality disorder. Thus, although a person with Bleulerian simple schizophrenia might satisfy the *DSM-III-R* criteria for schizotypal personality disorder, the diagnosis fails to capture the accompanying amotivation or the downward trajectory expected in simple schizophrenia. The concept of simple deterioration was rejected, but the debate about how to properly classify such persons continues.

FUTURE DIRECTIONS

A task force has now been formed to revise *DSM-III-R* diagnostic categories in preparation for *DSM-IV*, tentatively scheduled for release in 1992. Although the concept of simple schizophrenia was rejected in revising *DSM-III*, the Schizophrenia Work Group formed to review schizophrenia spectrum disorders is interested in reconsidering it (N. Andreasen, personal communication, October 1988). The original formulation of simple schizophrenia—that of a nonpsychotic illness with a deteriorating course and accompanied by features suggesting unusual affect, speech, or thinking—is not encompassed by any *DSM-III-R* diagnosis. The closest equivalents in *DSM-III-R* appear to be chronic schizophrenia, residual type, and schizotypal personality. These categories do not include the nonpsychotic, deteriorated state, however. In fact, a patient with residual schizophrenia has, by definition, experienced an "active phase" of schizophrenia characterized by the psychotic symptoms outlined in criterion A. Schizotypal personality disorder, on the other hand, captures the sense of oddity in affect, speech, or thought and impairment of social or occupational functioning, but not the deterioration. Traditionally, personality disorders have been conceptualized as stable, enduring, and maladaptive but not leading to marked deterioration of functioning in areas such as work, social relations, and self-care—the symptoms required in criterion B for the diagnosis of schizophrenia.

Apart from its delimitation from other disorders, several reasons exist for restoration of the simple schizophrenia diagnosis: 1) there are historic precedents for the disorder, 2) there is evidence for its genetic relatedness to core schizophrenia, 3) simple and core schizophrenia are similar descriptively and clinically, and 4) research emphasizing the schizophrenia spectrum would benefit from an operational definition of simple schizophrenia. Clearly, criteria need to be developed, and research assessing the reliability and validity of the syndrome needs to be conducted. Without compelling data, however, simple schizophrenia should not be included in a diagnostic manual.

We now propose criteria for simple schizophrenia (see appendix 1). The criteria are a modification of those currently used to define schizophrenia. We have simply omitted criterion A, which requires psychotic phenomena, and have modified criterion D (our criterion A) to require four of nine prodromal or residual symptoms rather than two symptoms. The reason for the latter change is to make the diagnostic category more restrictive than it is when only two symptoms are required. We have added schizotypal personality as an exclusion criterion (criterion F); mood disorders, autism, and organic disorders remain as exclusion criteria. The criteria are consistent with the original definitions of simple schizophrenia that Diem, Bleuler, and Kraepelin described. Each had emphasized the fundamental and not the accessory symptoms of schizophrenia. In modern parlance, simple schizophrenia is a syndrome of negative or defect symptoms but not positive or psychotic symptoms (36).

CONCLUSIONS

We have traced the origins of the concept of simple schizophrenia to the late nineteenth century, when European descriptive psychiatrists initially identified the syndrome of simple primary dementia. Simple schizophrenia was later elaborated by Diem and Bleuler and accepted by Kraepelin.

Use of the category flourished over the next half-century, and the syndrome was incorporated into widely used textbooks of psychiatry, although no new information had been learned since its early description. Rumblings of discontent arose, but not until the development of *DSM-III* was the disorder dropped from official American classification. Criticism had focused on its unclear and changing definition, its infrequent use, its poor reliability, and its doubtful descriptive validity. However, the original definition is still of heuristic interest. As the concept is not fully captured by any current *DSM-III-R* category, we propose operational criteria for simple schizophrenia and recommend that they be used to amass data to determine the validity of its inclusion as a category in *DSM-IV*.

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APPENDIX 1. Proposed Criteria for Simple Schizophrenia (Simple Deteriorated State)

A. Presence of four or more of the following symptoms:
  1. Marked social isolation or withdrawal
  2. Marked impairment in role functioning as wage earner, student, or homemaker
  3. Markedly peculiar behavior (e.g., collecting garbage, talking to self in public, hoarding food)
  4. Marked impairment in personal hygiene and grooming
  5. Blunted or inappropriate affect
  6. Digressive, vague, overly elaborate, or circumstantial speech, or poverty of speech, or poverty of content of speech
  7. Odd beliefs or magical thinking, influencing behavior and inconsistent with cultural norms (e.g., superstitiousness, belief in clairvoyance, telepathy, "sixth sense," "others can feel my feelings," overvalued ideas, ideas of reference)
  8. Unusual perceptual experiences (e.g., recurrent illusions, sensing the presence of a force or person not actually present)
  9. Marked lack of initiative, interest, or energy
B. Continuous signs of the disturbance for at least 6 months
C. During the course of the disturbance, functioning in areas such as work, social relations, and self-care is markedly below the highest level achieved before the onset of the disturbance (or, when the onset is in childhood or adolescence, failure to achieve expected level of social development)
D. Has never met criterion A for schizophrenia during the course of the disturbance
E. Schizoaffective disorder and mood disorder have been ruled out (i.e., if a major depressive or manic symptom has ever been present, the total duration of all episodes of a mood symptom has been brief relative to the total duration of the disturbance)
F. Schizotypal personality disorder has been ruled out (e.g., there is clear evidence of marked deterioration in functioning from the highest achieved in areas such as work, social relations, and self-care)
G. It cannot be established that an organic factor initiated and maintained the disturbance
H. There is no history of autistic disorder

Cognitive-Behavioral Treatment of Depressed Inpatients: Six- and Twelve-Month Follow-Up

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The authors report 6- and 12-month follow-up data for 45 depressed inpatients who were randomly assigned to either standard treatment (hospital milieu therapy, pharmacotherapy, clinical management sessions), cognitive therapy plus standard treatment, or social skills training plus standard treatment. All treatments began in the hospital and continued for 4 months after discharge on an outpatient basis. Significantly higher proportions of the patients who received additional cognitive-behavioral treatment (cognitive therapy or social skills) had responded by the end of the formal treatment period and did not relapse for the remainder of the 1-year follow-up period.

(Am J Psychiatry 1989; 146:1274–1279)

A number of psychotherapies that can be described as cognitive-behavioral have been found to be effective treatments for depressed outpatients (1–8), producing at least as much improvement as was produced by pharmacotherapy (1–10). Combining cognitive-behavioral treatment with pharmacotherapy has been found to result in higher response rates in some studies (2, 5) but equivalent rates in others (3, 4, 9, 11).

Since depression tends to be a recurrent disorder, perhaps the most important criterion for evaluating the efficacy of treatments for depression is the effect of treatment on long-term course. Unfortunately, due to the expense and difficulty of conducting long-term follow-up, there have been few reports of the long-term effectiveness of different treatments. The available studies have generally reported that depressed patients who received cognitive-behavioral treatment had better long-term outcome than did those who received pharmacotherapy alone (12, 13). Interpretation of these studies is hampered by 1) discontinuation of medications in the pharmacotherapy groups at the end of the treatment phase rather than continuation in a maintenance fashion and 2) differences in methods for describing the course of treated patients.

In addition, all of the studies cited here have been conducted with outpatients and have excluded patients who were hospitalized or who had a substantial suicide risk. Since depressed inpatients represent a substantial proportion of depressed patients and have considerably greater treatment costs, studies of more severely depressed patients are particularly important. Although there have been uncontrolled reports concerning the utility of cognitive-behavioral treatments for depressed inpatients (14, 15), our previous report (16) was the first well-controlled study that investigated the efficacy of cognitive-behavioral treatments with this type of patient.

In our previous study (16), depressed inpatients were randomly assigned to 1) standard treatment consisting of hospital milieu therapy, pharmacotherapy, and brief supportive contacts with a psychiatrist, 2) cognitive therapy, which consisted of standard treatment plus cognitive therapy (17), and 3) social skills training, which consisted of standard treatment plus social skills training (18, 19). All treatments began in the hospital and continued for 20 weeks on an outpatient basis. As reported in detail elsewhere (16), the results of this study indicated that cognitive therapy plus standard treatment and social skills training plus standard treatment produced significantly lower levels of symptoms and greater percentages of re-

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sponders than standard treatment alone at the end of the treatment phase. Thus, this previous report provided preliminary evidence that adding cognitive-behavioral treatments to the usual hospital treatment and pharmacotherapy can produce significant short-term benefits.

In this article we report the long-term outcome in our study of cognitive-behavioral treatments for depressed inpatients.

METHOD

Treatment Study

The subjects were 46 patients who had been admitted to a private psychiatric hospital. Inclusion criteria were 1) diagnosis of major depressive disorder according to the Diagnostic Interview Schedule (20), 2) Beck Depression Inventory (21) score greater than 17, 3) Modified Hamilton Rating Scale for Depression (17-item) (22) score greater than 17, and 4) age between 18 and 65 years. Exclusionary criteria included 1) a concurrent diagnosis of bipolar disorder, alcohol dependence or drug dependence, schizophrenia, somatization disorder, antisocial personality disorder, or organic brain syndrome, 2) medical illness of a type or severity that might contraindicate administration of tricyclic antidepressants or might produce substantial depressive symptoms, and 3) recent use of medication known to result in depressive symptoms.

The patients were randomly assigned to one of three treatment conditions: 1) standard treatment, 2) cognitive therapy plus standard treatment, or 3) social skills training plus standard treatment. All treatments began while the patient was in the hospital and continued for 20 weeks after discharge. Standard treatment was composed of the usual hospital milieu therapy, brief contacts with a psychiatrist, and antidepressant medication administered according to a semistructured medication protocol.

According to the medication protocol, patients were to receive one of two antidepressants thought to act on different neurotransmitter systems (amitriptyline and desipramine) at a dose of at least 150 mg/day. There was no upper limit on medication dose. Psychiatrists were free to choose between these two antidepressants on the basis of their own clinical judgment and the patient's previous treatment response and current symptoms. Other types of medications (neuroleptics and antianxiety agents) could be used as clinically indicated. Since the patients in this study tended to be treatment resistant along a number of dimensions, deviations from this basic medication protocol were allowed under the following conditions: 1) if the treating psychiatrist judged that the patient had not adequately responded (by current course or history) to an appropriate medication trial (250 mg or greater for 3 weeks) of each of these antidepressants, or 2) if side effects occurred that were of sufficient severity (by current course or history) to prevent attainment of adequate dose levels. The initial deviation allowed in these circumstances was either use of another tricyclic antidepressant of the treating psychiatrist's choice or use of suboptimal doses (less than 150 mg/day) when the side effects prevented attainment of an adequate dose and the patient had exhibited an adequate treatment response. Finally, if a patient had not responded after adequate trials of three different antidepressants or was unable to tolerate the side effects of at least three antidepressants and the treating psychiatrist felt that pharmacological treatment was no longer clinically necessary, no further pharmacological treatment was given. Once the patient's condition stabilized, all medications were continued for the duration of the active treatment phase of the project.

The cognitive therapy group received individually administered cognitive therapy (17) plus the standard treatment already described. The social skills training group received individually administered social skills training (18, 19) plus standard treatment. The medication plus management sessions occurred daily while the patients were in the hospital and five to six times during the outpatient phase. The psychotherapy sessions occurred five times a week during the inpatient stay and weekly during the outpatient phase.

Assessments of depressive symptoms, dysfunctional cognitions, social skills, and personality were conducted before initiation of treatment and at the end of treatment (24 weeks). Additionally depressive symptoms were assessed at discharge from the hospital (4 weeks) and at the midpoint of outpatient treatment (12 weeks).

Follow-Up Study

The follow-up was naturalistic. After termination of the active phase of treatment, all patients judged to be in need of further treatment and/or who desired further treatment were referred to appropriate clinical services. Our research staff maintained contact with patients through bimonthly telephone calls and occasionally provided treatment referral information but provided no further clinical services.

Although several previous studies (12, 14) have focused their follow-up analyses exclusively on those patients who responded to treatment during the treatment phase of the project, we think that the long-term outcome of nonresponders is relevant, particularly in a chronically depressed sample such as ours. It is certainly possible that the benefits of a particular treatment would manifest themselves after the official termination of the formal treatment phase. Although subsequent treatment and/or spontaneous remission may serve to dilute or mask potential long-term effects of treatment among patients who had initially not responded to treatment, finding long-term differences may be highly important. Thus, it seemed to us that to best describe all potential effects of treatment, the long-term outcome of all subjects should be included.

Since no significant differences were found between the cognitive therapy and social skills training conditions in short-term treatment response (16) and since preliminary analyses of the long-term follow-up data also yielded no significant differences between cognitive therapy and social skills training conditions, in the present report patients given these two types of therapy were combined into a "cognitive-behavioral" group to maximize clarity of presentation and statistical power. Thus, the comparisons reported in the remainder of this paper will be between subjects who received standard treatment alone and those who received standard treatment plus cognitive-behavioral psychotherapy.

Follow-up assessments were conducted 6 and 12 months after termination of treatment. In addition to these in-person assessments, interim assessments consisting of administration of the Modified Hamilton Rating Scale for Depression by telephone were conducted every 8 weeks for the first 6 months of follow-up and every 12 weeks for the second 6 months. During these interim assessments, patients were instructed to respond according to their worst period since the previous assessment, thus providing a continuous measure of symptom severity.

To address the issue of treatment response, this report focuses on depressive symptoms that were assessed by the Modified Hamilton Rating Scale for Depression and the Beck Depression Inventory. We also report data concerning suicidal ideation and attempts, as assessed by a modified version of the Scale for Suicidal Ideation (23). Data analysis will be limited to the 6- and 12-month assessments, although the interim Modified Hamilton Rating Scale for Depression assessments administered by telephone were used when defining recovery, relapse, and remission. Data concerning other variables will be reported in subsequent reports.

Recovery was defined as a Modified Hamilton Rating Scale for Depression score less than 7, a Beck Depression Inventory score less than 9, and a Scale for Suicidal Ideation score less than 7 during the active treatment phase. Relapse was defined as meeting the criteria for recovery during the treatment phase of the project followed by the occurrence of any of the following criteria during the follow-up period: 1) a Modified Hamilton Rating Scale for Depression score greater than 17, 2) a Beck Depression Inventory score greater than 16, 3) a Scale for Suicidal Ideation score greater than 7, or 4) rehospitalization due to psychiatric symptoms. To provide an overall measure of treatment response, remission was defined as meeting criteria for recovery during the treatment phase and not meeting criteria for relapse during the entire follow-up period. Since the optimal goal of any treatment is to produce long-term remission of symptoms, the proportion of patients who achieved remission is perhaps the best overall measure of treatment effectiveness. The proportion of patients who achieved recovery and who achieved remission were calculated separately for the patients who completed treatment and for all patients who entered treatment.

It should be noted that although previous studies have generally considered subsequent outpatient treatment as an indication of relapse, we chose not to include subsequent outpatient treatment in our criteria for relapse and remission. In our view, subsequent outpatient treatment may not be a negative outcome at all but may be a quite positive result, especially with more severely depressed patients. For example, Prien and Kupfer (24) reported that maintenance doses of antidepressants are necessary for at least 16–20 weeks after recovery to prevent relapse. Similarly, from a psychosocial perspective, for a patient with chronic marital and/or family difficulties who has previously denied or been unwilling or unable to work on these problems, subsequent marital and/or family treatment may represent an important positive outcome. In view of the possible positive connotations, we chose not to include subsequent outpatient treatment as a criterion for relapse but to report this variable separately.

Since, as we reported elsewhere (16), standard treatment and cognitive-behavioral treatment plus standard treatment differed significantly in pretreatment levels of four variables (SCL-90 positive symptom total and somatization scale, Social Adjustment Scale, and Interpersonal Dependency Scale), all analyses of continuous variables were conducted by using analysis of covariance with these variables as covariates. Chi-square comparisons were used for categorical comparisons. Since we hypothesized that adding cognitive-behavioral treatment would produce improved response rates and had no expectation that the addition of cognitive-behavioral treatment would produce negative effects, one-tailed comparisons were used.

RESULTS

Summary of Treatment Phase Results

One patient was dropped from the study due to the onset of a manic episode and was not included in any analyses. As can be seen in table 1 and in more detail in our previous report (16), the patients receiving standard treatment alone and the patients receiving additional cognitive-behavioral treatment did not differ from each other in demographic characteristics, measures of depression, or treatment variables. Significantly more of the patients who received standard treatment alone than of patients who received additional cognitive-behavioral treatment dropped out of treatment (seven [41%] of 17 patients versus five [18%] of 28 patients) ($\chi^2=2.9$, df=1, $p<0.05$).

There were no significant differences between groups in levels of depressive symptoms or percentage of responders at the end of hospitalization.

TABLE 1. Demographic and Treatment Characteristics of 45 Depressed Patients Given Standard Treatment Plus Cognitive-Behavioral Treatment or Standard Treatment Alone[a]

Characteristic	Patients Given Cognitive-Behavioral Treatment (N=28)	Patients Given Standard Treatment (N=17)
Sex		
Male		
Number	9	2
Percent	32	12
Female		
Number	19	15
Percent	68	88
Age (years)		
Mean	35.3	37.4
SD	12.3	13.9
Number of previous episodes		
Mean	6.5	7.2
SD	10.2	9.5
Age at onset (years)		
Mean	25.1	24.7
SD	14.6	15.8
Attempted suicide before admission		
Number	5	5
Percent	18	29
Modified Hamilton Rating Scale for Depression score		
Mean	23.6	22.6
SD	3.7	3.7
Beck Depression Inventory score		
Mean	28.2	29.2
SD	6.1	7.5
Scale for Suicidal Ideation score		
Mean	5.9	12.5
SD	10.1	14.8
Had diagnosis of dysthymia		
Number	15	6
Percent	54	35
Had diagnosis of melancholia		
Number	8	6
Percent	29	35
Length of hospital stay (days)		
Mean	27.3	23.4
SD	8.6	8.2
Number of medication and management sessions		
Mean	26.5	24.9
SD	6.1	5.9
Received medication (≥150 mg/day)		
Number	19	13
Percent	69	76
Received medication (<150 mg/day)		
Number	6	3
Percent	21	18
Did not receive medication		
Number	3	1
Percent	11	6
Number of cognitive therapy sessions		
Mean	28.5	—
SD	5.8	—

[a] Standard treatment included hospital milieu therapy, pharmacotherapy, and clinical management sessions. Cognitive-behavioral treatment included cognitive therapy and social skills training. All comparisons between groups were nonsignificant according to one-tailed chi-square tests.

At the end of the formal treatment phase of the project, analyses of covariance indicated that the 23 subjects given additional cognitive-behavioral treatment who completed treatment had significantly lower scores on the Beck Depression Inventory ($F=4.7$, $df=1, 26$, $p<0.05$) but not on the Modified Hamilton Rating Scale for Depression than did the 10 subjects given standard treatment alone who completed treatment (see table 2). When the entire sample was included in the end-point analysis, the 28 subjects given additional cognitive-behavioral treatment also had significantly lower Beck Depression Inventory scores ($F=7.4$, $df=1, 38$, $p<0.01$) and almost significantly lower scores on the Modified Hamilton Rating Scale for Depression ($F=3.4$, $df=1, 38$, $p<0.10$) than did the 17 subjects given standard treatment alone (see table 2).

During the active treatment phase, a significantly greater percentage of the patients who completed cognitive-behavioral treatment (20 [87%] of 23 patients) than of those who completed standard treatment (six [60%] of 10 patients) recovered ($\chi^2=3.0$, $df=1$, $p<0.05$). Similar results were found when all subjects who entered treatment were considered (20 [71%] of 28 patients versus six [35%] of 17 patients) ($\chi^2=5.7$, $df=1$, $p<0.01$).

Follow-Up Phase

Six- and 12-month follow-up data were collected on 31 (94%) of the 33 patients who completed treatment: 22 of the patients given additional cognitive-behavioral treatment and nine of those given standard treatment alone. Including all interim assessments, we successfully completed 227 (82%) of 276 possible assessments.

Approximately three-quarters of our sample received additional outpatient treatment during the follow-up period. The two treatment conditions did not differ in the proportion of patients receiving additional treatment (16 [73%] of the patients given additional cognitive-behavioral treatment versus seven [78%] of the patients given standard treatment alone). Five (16%) of the 31 patients were rehospitalized. The patients given additional cognitive-behavioral treatment did not differ significantly from those given standard treatment alone in percentage of patients rehospitalized (three [14%] versus two [22%]).

No patient attempted suicide during the course of the follow-up. Eight (26%) of the 31 patients had significant suicidal ideation (Scale for Suicidal Ideation score greater than 7) during the follow-up. There were no significant differences between treatment conditions in either Scale for Suicidal Ideation scores (see table 2) or in the proportion of patients having substantial suicidal ideation (six [27%] of the 22 patients given additional cognitive-behavioral treatment versus two [22%] of the nine patients receiving standard treatment alone).

Although there was some tendency for the cognitive-

TABLE 2. Outcome Data for 45 Depressed Patients Given Standard Treatment Plus Cognitive-Behavioral Treatment or Standard Treatment Alone[a]

Measure	Patients Given Cognitive-Behavioral Treatment			Patients Given Standard Treatment		
	N	Mean	SD	N	Mean	SD
Beck Depression Inventory score						
End of treatment						
Patients who completed treatment	23	7.1	11.6	10	11.2	7.3
All patients	28	11.2	13.5	17	19.1	14.8
6-month follow-up	22	8.0	7.8	9	8.5	8.5
12-month follow-up	22	4.6	4.3	9	12.0	12.8
Modified Hamilton Rating Scale for Depression score						
End of treatment						
Patients who completed treatment	23	7.3	8.4	10	7.8	7.6
All patients	28	8.7	8.5	17	12.4	10.0
6-month follow-up	22	8.2	7.8	9	9.6	9.0
12-month follow-up	22	6.6	6.2	9	9.7	12.3
Scale for Suicidal Ideation score						
End of treatment	28	8.4	13.1	17	5.2	11.3
6-month follow-up	22	5.2	4.4	9	2.6	5.1
12-month follow-up	22	5.1	4.6	9	6.5	7.8

[a] Standard treatment included hospital milieu therapy, pharmacotherapy, and clinical management sessions. Cognitive-behavioral therapy included cognitive therapy and social skills training.

behavioral group to have lower levels of depression, analyses of covariance yielded no significant differences in Modified Hamilton Rating Scale for Depression or Beck Depression Inventory scores between treatment conditions at either the 6- or 12-month follow-up assessment (see table 2).

Of the 26 patients who recovered during the treatment phase, seven (27%) relapsed. There was a nonsignificant trend for the patients given standard treatment alone (three [50%] of six patients) to have a higher rate of relapse than the patients given additional cognitive-behavioral treatment (four [20%] of 20 patients) ($\chi^2=1.9$, df=1, $p<0.10$).

Overall Treatment Response

Of the 31 patients who completed treatment, 18 (58%) maintained their recovery through the entire follow-up period and were classified as having achieved remission. A significantly higher percentage of patients given additional cognitive-behavioral treatment (15 [68%] of 22) than of patients given standard treatment alone (three [33%] of nine) achieved remission ($\chi^2=3.2$, df=1, $p<0.05$). When all patients who entered treatment were considered, the advantage for cognitive-behavioral treatment was even more striking: 54% versus 18% ($\chi^2=5.6$, df=1, $p<0.01$).

DISCUSSION

In combination with our previous report, the results of this study represent the first well-controlled study on the utility of cognitive-behavioral treatment for depressed inpatients. Overall, the results suggest that adding cognitive-behavioral treatments to a "standard" treatment regimen of pharmacological treatment and brief supportive contact produces additional benefits for severely depressed patients. Although no superior benefits were found during hospitalization itself, by the end of the formal treatment period (20 weeks after discharge), the patients who received additional cognitive-behavioral treatment had lower levels of depressive symptoms and higher rates of recovery than the patients who received standard treatment alone. In the follow-up reported here, the patients receiving additional cognitive-behavioral treatment had a nonsignificant tendency to have lower rates of relapse and had a significantly higher proportion of patients who achieved remission (patients who recovered by the end of the formal treatment period and did not relapse for the remainder of the follow-up). Thus, the addition of the cognitive-behavioral treatment appeared to produce both short- and long-term advantages in recovery and maintenance of recovery from a depressive episode.

Comparisons between this study and previous studies are difficult due to substantial differences between studies in their subjects, methods, and analysis of follow-up results. More specifically, the present study differed methodologically from previous studies in 1) use of a severely depressed inpatient sample, 2) longer and more intensive treatment intervention, and 3) use of a semistructured medication protocol. It also differed from previous follow-up studies in the inclusion of both initial responders and nonresponders and differences in criteria for defining relapse and remission. Despite these differences from previous studies, the rates of relapse and remission in this study, in general, appear similar to those of other studies (8, 12).

In addition to documenting the advantages of adding cognitive-behavioral treatment, it is important to discuss the areas in which adding cognitive-behavioral treatment did not make a difference. Level of suicidal ideation is perhaps the most important variable in this category. We found no differences between the treatments in mean levels of suicidal ideation or in the percentage of patients with substantial suicidal ideation. In fact, over 20% of the patients in both treatment conditions had substantial levels of suicidal ideation. When these percentages are compared with the 32% who had substantial suicidal ideation before the study (16), the unavoidable conclusion is that none of our treatments were very effective in reducing levels of suicidal ideation. Also associated with these subsequent levels of suicidal ideation was a substantial rehospitalization rate (16%). The lack of reduction in suicidal ideation has important clinical implications and suggests that clinical researchers need to look beyond standard treatment packages for successful treatment of suicidal patients.

We also found no differences between treatment groups in level of depression at the 6- and 12-month assessments or in the percentage of patients who entered subsequent outpatient treatment. The lack of symptom differences at follow-up may reflect an overall tendency to improve during the follow-up period as well as the effectiveness of the subsequent treatment. The finding that a majority of depressed inpatients appear to require additional treatment beyond the 24-week treatment trial used in this study is in direct contrast to outpatient trials in which a majority of depressed outpatients responded to a 12–16-week treatment trial and did not require subsequent treatment. As we have already argued in this paper, interpretation of subsequent outpatient treatment is difficult. Although subsequent treatment may indicate an incomplete recovery, it may also indicate an increased willingness or capacity to address some major problematic areas in the patient's life. Regardless of whether subsequent outpatient treatment is viewed as a negative or positive outcome, our data suggest that the type of severely depressed patient treated in this study requires a greater amount of treatment than do the depressed outpatients treated in previous studies.

In conclusion, although the current study has some limitations due principally to the small sample size, the similarities in results between our long-term outcome data and several previous studies add greater confidence to the generalizability of the results. In combination with other studies (11), our study suggests an overall incremental benefit of adding cognitive-behavioral treatment to standard treatment with pharmacotherapy alone. Of particular importance is that this study has extended these results concerning the efficacy of combination treatment to a severely depressed inpatient sample.

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Risk of Schizophrenia in Character Disordered Patients

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Inpatients from the Chestnut Lodge follow-up study diagnosed with character disorder were studied to predict future schizophrenic decompensation. Individually, three DSM-III *criteria for schizotypal personality disorder predicted schizophrenia at long-term follow-up: magical thinking, suspiciousness or paranoid ideation, and social isolation. Additionally, lower IQ, poorer premorbid quality of work, and transient delusional experiences were predictive. No borderline personality disorder criterion was predictive. This suggests that schizotypal but not borderline personality disorder belongs in the schizophrenic spectrum. Within schizotypal personality disorder, criteria from both familial and clinical traditions appear to be dimensions of vulnerability to psychosis.*

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Rado (1) first proposed the term "schizotypal" in 1953 as shorthand for the term "schizophrenic phenotype": an ensemble of character traits hypothesized to be present throughout life and to mark a genetic or inherited predisposition to schizophrenia. Affected individuals were thought to manifest "core behavioral traits" related to schizophrenia and to be vulnerable to decompensating into manifest psychosis when subject to particularly unfavorable environmental influences (2).

Studies aiming to determine what clinical features best characterize this putative disorder have followed either a familial or a clinical tradition (3). The familial approach derives from efforts to characterize nonpsychotic relatives of schizophrenic individuals who might represent phenotypic variants in the expression of the schizophrenic genotype. Features included in the *DSM-III* criteria for schizotypal personality disorder evolved from the attempt of Spitzer et al. (4) to operationalize "borderline schizophrenia," a syndrome found to be prevalent among the relatives of probands in the Danish adoption study. The *DSM-III* criteria for schizotypal personality disorder include eight clinical features: 1) magical thinking, 2) ideas of reference, 3) social isolation, 4) recurrent illusions or depersonalization, 5) odd speech, 6) inadequate rapport, 7) suspiciousness or paranoid ideation, and 8) undue social anxiety. There is considerable evidence that these criteria, as a set, identify individuals found significantly more frequently among the biological relatives of schizophrenic patients than among relatives of matched control subjects (5–7).

Siever and Gunderson (8) subdivided the individual criteria for schizotypal personality disorder into items reflecting cognitive and/or perceptual dysfunction (magical thinking, ideas of reference, recurrent illusions or depersonalization, odd speech, and suspiciousness or paranoid ideation) and items indicative of poor social and/or interpersonal functioning (social isolation, inadequate rapport, and undue social anxiety). Kendler et al. (3, 9) divided the criteria into groups of items representing mild forms of negative symptoms (social isolation, odd speech, inadequate rapport, suspiciousness or paranoid ideation, and, possibly, undue social anxiety) and positive symptoms (magical thinking, ideas of reference, and recurrent illusions or depersonalization). Explorations of the usefulness of individual symptoms of schizotypal personality disorder in discriminating relatives of schizophrenic patients have tended to place greater emphasis on the social and/or interpersonal and negative symptoms than on the cognitive and/or perceptual or positive symptoms (9, 10).

Since schizotypal relatives of schizophrenic patients rarely seek or receive psychiatric attention, the clinical utility of defining the concept on the basis of family studies has been questioned (11). In contrast to the familial approach, a clinical tradition has focused on describing individuals in clinical populations who seem to demonstrate "attenuated" or "subclinical" forms of schizophrenia without overt psychosis or functional deterioration. In clinical settings, the *DSM-III* cognitive-perceptual schizotypal items appear at

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least as useful as the social-interpersonal features in identifying patients receiving treatment (11–13).

Long-term follow-up data on systematically defined groups of schizotypal patients were not available until comparatively recently (14). Accordingly, the extent to which current definitions of schizotypal personality disorder are associated with future vulnerability to schizophrenia is unknown. Nevertheless, knowledge of the dimension of longitudinal course could be valuable in establishing the validity of different schizotypal criteria and concepts. In this paper we describe an empirical effort to determine which clinical features are associated with a risk of developing future schizophrenia among a heterogeneous sample of inpatients with severe character disorders. These patients were hospitalized in a long-term residential setting, retrospectively rediagnosed according to current criteria, and reevaluated an average of 15 years following their discharge as part of the Chestnut Lodge follow-up study (15, 16).

METHOD

The follow-up study setting, methods of baseline assessment, and concurrent outcome evaluations have been outlined elsewhere (15, 16). Included in the present study were all patients who received a baseline research diagnosis of borderline personality disorder and/or schizotypal personality disorder and for whom follow-up data were available ($N=105$). Patients with borderline personality disorder ($N=75$) met at least four of the *DSM-III* criteria for borderline personality disorder and/or at least six of the Gunderson and Kolb (17) criteria for borderline personality disorder. The patients with schizotypal personality disorder ($N=30$) met at least three of the *DSM-III* criteria for schizotypal personality disorder. Patients with a comorbid axis I major psychotic or affective disorder were not included in the present sample.

Patients were located and interviewed an average of 15 years following discharge from the index hospitalization. All patients were given a follow-up clinical diagnosis by one of us (T.H.M.) on the basis of their subsequent course and outcome following discharge. Outcome ratings and follow-up diagnoses were made independent of knowledge of admission diagnosis and clinical picture. Among the 105 patients diagnosed as having character disorders during the index hospitalization, 17 (16%) received a follow-up diagnosis of schizophrenia and one (1%) received a follow-up diagnosis of schizoaffective disorder. Since the course and outcome for these two axis I disorders appeared quite similar in our group of patients (18), these groups were collapsed and all 18 patients (17%) were considered to have a schizophrenic outcome.

In assigning a follow-up diagnosis of schizophrenia, some evidence of positive psychotic symptoms, long-term functional incapacities, and the absence of substantial cyclicity were required. Patients demonstrating positive psychotic symptoms, functional compromise, and prominent affective features were diagnosed as having schizoaffective disorder. Although follow-up diagnoses were essentially clinical rather than systematic, it was possible to test their validity by comparing the 18 patients with a follow-up diagnosis of schizophrenia with 160 patients who had been systemically assigned a *DSM-III* admission diagnosis of probable or definite schizophrenia. The functional outcomes of these two groups were not significantly different in the domains of hospitalization, work, severity of symptoms, social functioning, and global outcome, strongly suggesting that the follow-up diagnoses of schizophrenia were valid. This is not surprising, since the elements used for the follow-up clinical diagnoses (19) are the core features of schizophrenia as defined operationally in *DSM-III.*

Each individual *DSM-III* item for schizotypal personality disorder and borderline personality disorder and each Gunderson and Kolb (17) item for borderline personality disorder was evaluated to assess its ability to predict schizophrenia at follow-up. The chi-square statistic was used to evaluate these dichotomous variables. Significance was set at $p<0.05$.

In addition to evaluating existing criteria, we wished to determine whether any baseline clinical features not included in the diagnostic criteria were useful in predicting a follow-up diagnosis of schizophrenia. Accordingly, a total of 92 additional variables grouped in six "families" were screened as potential predictors. For this analysis, the 18 patients with a schizophrenic outcome were compared with the 87 patients who did not receive a follow-up diagnosis of schizophrenia across three demographic, seven family, two index hospitalization, nine illness onset, 12 premorbid-prognostic, and 59 sign and symptom variables. A more complete description of these variables, rated on the basis of information available up to and including the index admission, has been reported elsewhere (15). Since a multivariable screening process was used to evaluate features not included in the diagnostic criteria, the Bonferroni inequality was applied to offset the probability of chance findings of significance (20). Individual alpha levels were set for variables in each "family" by dividing 0.05 by the number of variables in the "family."

To determine the strongest overall predictive set, all individual variables found in univariate analyses to be associated with a schizophrenic outcome at a level of $p\leq 0.05$ were entered into multiple regression and stepwise linear discriminant function analyses.

RESULTS

Only four (22%) of the 18 patients with a schizophrenic outcome met at least four *DSM-III* criteria for schizotypal personality disorder at index admission. The study criteria of at least three *DSM-III* criteria for schizotypal personality disorder, however, was quite

TABLE 1. Schizotypal Features as Predictors of Follow-Up Diagnoses of Schizophrenia Among 105 Hospitalized Patients With Character Disorder

Clinical Feature	Schizophrenia (N=18)		No Schizophrenia (N=87)		Base Rate (%)[a]	Specificity (%)[b]	Positive Predictive Power (%)[c]	Negative Predictive Power (%)[d]	χ^2 (df=1)	p
	N	%	N	%						
DSM-III schizotypal features										
Magical thinking	6	33	3	3	9	97	67	88	13.40	<0.0003
Ideas of reference	2	11	13	15	14	85	13	82	0.96	n.s.
Social isolation	15	83	39	45	51	55	28	94	7.38	<0.007
Recurrent illusions or depersonalization	1	6	17	20	17	80	6	81	1.18	n.s.
Odd speech	4	22	13	15	16	85	24	84	1.70	n.s.
Inadequate rapport	4	22	19	22	22	78	17	83	0.00	n.s.
Suspiciousness or paranoid ideation	8	44	14	16	21	84	36	88	5.63	<0.02
Undue social anxiety	10	56	38	44	46	56	21	86	0.44	n.s.
Brief or atypical delusional experiences	6	33	3	3	9	97	67	88	13.40	<0.0003

[a] Base rate=proportion of all patients with character disorder who had the symptom.

[b] Specificity=proportion of patients with character disorder without a schizophrenic outcome who did not have the symptom.

[c] Positive predictive power=proportion of patients with the symptom who had a schizophrenic outcome (conditional probability of schizophrenic outcome given presence of symptom).

[d] Negative predictive power=proportion of patients without the symptom who did not have a schizophrenic outcome (conditional probability of nonschizophrenic outcome given absence of the symptom).

effective in identifying patients at risk for decompensation: 67% (N=12) of the 18 patients with a schizophrenic outcome but only 21% (N=18) of the 87 patients without a schizophrenic outcome met the study criteria for schizotypal personality disorder at index admission ($\chi^2=15.45$, df=1, $p<0.0001$). Of the six remaining patients with a schizophrenic outcome, two met at least five *DSM-III* criteria for borderline personality disorder, two met at least four *DSM-III* criteria for borderline personality disorder, and two met at least seven Gunderson and Kolb (17) criteria for borderline personality disorder at index admission. Correspondingly, at baseline the 18 patients with a schizophrenic outcome demonstrated significantly more total *DSM-III* schizotypal items (mean±SD) than did the 87 patients without a schizophrenic outcome (2.8±1.2 versus 1.8±1.4; t=2.80, df=103, $p<0.006$). The 18 patients with a schizophrenic outcome also had fewer total *DSM-III* borderline personality disorder items (3.6±1.5 versus 4.3±1.5; t=−2.06, df=103, $p<0.04$) and fewer Gunderson and Kolb (17) borderline personality disorder items (5.4±1.8 versus 6.4±1.7; t=−2.30, df=103, $p<0.02$) than the 87 patients without a schizophrenic outcome.

The sensitivity, specificity, positive predictive power, and negative predictive power of individual *DSM-III* schizotypal personality disorder items for predicting a schizophrenic outcome among our sample of patients with character disorders are shown in table 1. Three features, magical thinking, suspiciousness or paranoid ideation, and social isolation, were associated with future decompensation at a level of 0.05 or less. None of the *DSM-III* borderline personality disorder or Gunderson and Kolb (17) borderline personality disorder items were associated with a schizophrenic outcome at this level.

Among other clinical features screened as potential predictors, no demographic, family, index hospitalization, or illness onset variables were significantly associated with schizophrenia at follow-up. At the individual alpha level of 0.0008 (0.05 divided by 59), only one of 59 signs or symptoms not currently encompassed in *DSM-III* was found to be predictive. Patients with a schizophrenic outcome were more likely to have brief or atypical delusional experiences before or at admission. Examples of the latter include intermittent quasi-delusional concerns about good and evil, uncertain and intermittent feelings of having killed someone, and the transient, near-delusional belief (in a female patient) of being a man. The predictive utility of brief or atypical delusional experiences is included in table 1.

Among the 12 premorbid-prognostic features studied, patients with a schizophrenic outcome as a group demonstrated a significantly lower score on the composite Chestnut Lodge Prognostic Scale, a 12-point scale on which 12=best outcome (21). The patients with a schizophrenic outcome had a mean score of 6.8±1.8, compared with 8.6±2.2 for the patients without a schizophrenic outcome (t=−3.28, df=103, $p<0.001$). Although the univariate alpha for the premorbid-prognostic family did not meet the criterion of 0.004 (0.05 divided by 12), lower premorbid quality of work (2.0±0.9 versus 2.9±1.1 on a 0–4 scale on which 4=best quality; t=−2.79, df=87, $p<0.007$) and lower mean IQ (112±13 versus 119±10; t=

-2.35, df=83, $p<0.02$) later emerged in the regression equation (see below) as components of a highly discriminating set of variables predicting membership in the group of patients with a schizophrenic outcome.

The multiple regression equation derived following the entry of all the variables found significant at $p<0.05$ included the following individual variables, in order of the percent of variance explained: magical thinking, brief or atypical delusional experiences, social isolation, lower IQ, and poor premorbid work functioning. The equation was highly statistically significant ($F=15.12$, df=5, 99, $p<0.00001$) and accounted for nearly half of the outcome variance (multiple $R=0.66$, $R^2=0.43$). Stepwise linear discriminant function analysis correctly classified 67% of the patients with a schizophrenic outcome and 92% of the patients without a schizophrenic outcome.

DISCUSSION

Although vulnerability to future schizophrenic decompensation was a key element in the original concept of schizotypal personality disorder, to our knowledge this is the first empirical effort to study predictors of future schizophrenia among nonpsychotic patients with character disorders. The patients in our hospital sample demonstrated a relatively high risk for schizophrenia (17%) when followed over an average period of 15 years. In evaluating this finding, it is important to consider that Chestnut Lodge, as a tertiary care facility, usually accepts patients only after extensive previous treatment efforts have proven ineffective. On the average, patients with character disorders in this study had had symptoms 7.5±8.4 years before their index admission at age 27±9 years. As a group they averaged 2.3±2.2 previous hospitalizations and 22.8±35.0 months of previous outpatient treatment. Thus, they constituted a unique sample of patients who had established themselves as severely and chronically disabled. In retrospect, it may be that many of the patients with a schizophrenic outcome were in an early or prodromal phase of schizophrenia at the time of their index admission. It is unclear whether patients with character disorders in outpatient or acute inpatient facilities would demonstrate comparable risk.

Among our hospitalized patients with character disorders, we found three broad clinical elements that appear to constitute risk markers or vulnerability indicators of future schizophrenia. These include cognitive-perceptual distortions (magical thinking, brief or atypical psychotic experiences, and suspiciousness or paranoid ideation) and social-interpersonal dysfunction (social isolation). The third group of variables, IQ and premorbid skills, appears to represent general adaptive assets or deficiencies capable of modifying overall risk in either an upward or downward direction. These data provide validation for the concept of a vulnerable schizotypal personality and also point to the multidimensional nature of the processes underlying such vulnerability. Variables in each domain contributed independently to the overall variance explained.

Although the family history data for our patients were limited by reliance on medical records, we did not find a greater presence of schizophrenia in the families of patients with a schizophrenic outcome. This finding is consistent with the results of other studies in both clinical and familial samples (7, 13). Although schizotypal personality disorder is found in the biological families of schizophrenic probands, schizotypal but not schizophrenic individuals are found among the relatives of schizotypal probands. This may, in part, be explained by a lower prevalence of schizophrenia than of schizotypal personality disorder or by the possibility that current criteria only imperfectly define "true" schizotypal personality disorder (7).

To the extent that no *DSM-III* borderline personality disorder items were associated with future schizophrenia, the results presented here validate the association of schizotypal personality disorder, but not of borderline personality disorder, with the schizophrenic spectrum.

As currently conceptualized, *DSM-III* criteria for schizotypal personality disorder appear to include several important items predicting future schizophrenic decompensation. Other *DSM-III* schizotypal personality disorder items were not predictive, notably, odd speech, ideas of reference, recurrent illusions or depersonalization, undue social anxiety, and inadequate rapport. A reworking of the schizotypal personality disorder criteria de-emphasizing these elements but including brief or atypical psychotic experiences might maximize the usefulness of the criteria as a predictive as well as a diagnostic set. Although transient, broadly defined psychotic symptoms are often reported in borderline personality disorder (22–24), our data suggest that these clinical features may best serve as criteria for schizotypal personality disorder, not borderline personality disorder (25).

Whether familial or clinical considerations ought to be given primacy as validating criteria for the diagnosis of schizotypal personality disorder is currently under debate (3, 11–13, 25, 26). Our data suggest that the risk of schizophrenic decompensation, at least among hospitalized patients with character disorders, is greatest when the core features emphasized by each research tradition coexist in the same individual. The data are consistent with a clinical model positing that individuals manifesting a tendency toward cognitive distortions might "drift" in the direction of psychosis when these cognitive tendencies remain uncorrected by interpersonal feedback experiences over prolonged periods of social isolation. Clinically and phenomenologically one version of this process has been vividly described in terms of the elaboration of a "false self" that maintains distance from others, progressively isolates one from creative involvement with reality, and fosters withdrawal into fantasy. Under such circumstances the "actual" world for the person becomes shrunken and impoverished, fantasy blends into delusions, and reality testing, already tenuous, is lost (27, 28).

The probable heterogeneity of schizophrenia virtually guarantees that no single hypothesized etiological series of events explains more than a subgroup of cases. Nevertheless, our data lend support to the relevance of an interactive cognitive vulnerability/social isolation model in at least some cases.

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Study of 60 Patients With AIDS or AIDS-Related Complex Requiring Psychiatric Hospitalization

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Sixty patients with acquired immune deficiency syndrome (AIDS) or AIDS-related complex were treated on a locked inpatient psychiatric unit over a 30-month period. The wide range of mental disorders exhibited by these patients, key aspects of patient management, and the difficulty in psychiatric differential diagnosis are described.

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As the number of cases of acquired immune deficiency syndrome (AIDS) and AIDS-related complex grows, physicians are witnessing the neuropsychiatric complications of these illnesses and attempting to develop treatment strategies to combat them. Research by many authors (1–3) argues definitively that the human immunodeficiency virus (HIV) infects human nervous tissue. The psychiatric literature now contains many reports of individuals manifesting a variety of psychiatric complications of HIV infection, including adjustment disorders, psychosis, and organic mental disorders (4–8). This article presents a case series to illustrate the phenomenology of major psychiatric disturbances arising in patients with AIDS and AIDS-related complex.

METHOD

In July 1985 the Department of Psychiatry at San Francisco General Hospital centralized its psychiatric treatment of inpatients with AIDS and AIDS-related complex to promote their optimal care (9). Sixty patients were treated on one unit between July 1985 and December 1987. In a retrospective review of the records of their first admissions to the unit, data were gathered on psychiatric diagnosis, length of hospital stay, psychoactive medications prescribed at discharge, particular difficulties arising during inpatient management, and disposition. As the attending psychiatrist, I had made the psychiatric diagnoses according to *DSM-III*, but these were reviewed and are reported in accordance with *DSM-III-R* criteria.

Fifty-eight of the 60 patients were men and two were women. Their average age was 35 years (range=20–54). Fifty-five of the men were homosexual or bisexual, and 10 of these were intravenous drug users. The three heterosexual men and both women were also intravenous drug users. Forty-five patients were white and 15 were from ethnic minorities. Ninety percent (N=54) had been admitted involuntarily; this is comparable to the percentage of all patients (93%) admitted on an involuntary basis to all of the hospital's psychiatric units during the study period. All 60 patients were in group IV of the modified Centers for Disease Control classification of HIV infection (10); 37 patients had AIDS and 23 had AIDS-related complex.

The diagnostic assessments included detailed medical and psychiatric histories; careful mental status, physical, and neurological examinations; standard and additional laboratory evaluations (including CT or magnetic resonance imaging [MRI] of the head and lumbar puncture when not done recently and when allowed by patients); frequent consultation with other medical specialists; and, when possible, neuropsychological testing. Most patients' diagnoses of AIDS or AIDS-related complex had been established by their primary care physicians before admission; for three patients, however, the diagnosis was established during the psychiatric admission.

RESULTS

Although the majority of the patients demonstrated mixtures of psychopathology (e.g., one patient might have mood disturbance, concurrent substance abuse, mild cognitive dysfunction, and character pathology), a primary psychopathological process that caused and/or sustained the psychiatric hospitalization could be discerned for all 60. Table 1 lists the primary psychiatric diagnoses and summarizes the data, by diagnosis, on psychiatric history, length of stay, presence of cognitive deficits, discharge medications, and disposition.

Patients with major depression and those with adjustment disorders with depressed mood had hospital

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TABLE 1. Data on 60 Patients With AIDS or AIDS-Related Complex Requiring Psychiatric Hospitalization

Primary *DSM-III-R* Diagnosis			Time Since Diagnosis of AIDS/AIDS-Related Complex (months)		Length of Stay (days)		Patients With Prior Psychiatric Hospitalization		Patients With Mild Cognitive Deficits		Primary Discharge Medication
	N	%	Mean	Range	Mean	Range	N	%	N	%	
Depression	20	33	7	1–24	9	2–24	6	30	9	45	—
Adjustment disorder with depressed mood	13	22	4.5	1–24	10	2–24	5	38	6	46	None, 62%; benzodiazepine, 23%; antipsychotic, 15%
Major depression	7	12	11	2–24	7	4–17	1	14	3	43	Tricyclic, 57%; antipsychotic, 29%; none, 29%
Dementia	18[a]	30	8	0–36	35	6–152	2	11	0	0	—
With organic mood disorder, manic	3	5	7	4–11	66	15–152	1	33	0	0	Antipsychotic, 100%; lithium, 67%; clonidine, 33%
With organic mood disorder, depressed	9	15	9	4–36	57	6–152	0	0	0	0	Antipsychotic, 100%; none, 33%; tricyclic, 11%
With organic delusional syndrome	2	3	8	4–12	38	17–60	0	0	0	0	Antipsychotic, 100%; benzodiazepine, 50%
Without additional diagnosis	4	7	5	0–13	19	12–33	1	25	0	0	None, 75%; antipsychotic, 25%
Schizophrenia	6	10	4	0–12	10	3–22	6	100	6	100	Antipsychotic, 100%; benzodiazepine, 33%
Brief reactive psychosis	6	10	7	0–24	11	7–18	2	33	6	100	Antipsychotic, 100%
Bipolar disorder, manic	4	7	4	0–10	12	3–14	3	75	4	100	Antipsychotic, 50%; lithium, 50%
Stimulant-related psychosis	4	7	7	1–21	17	4–37	0	0	2	50	—
Amphetamine delusional disorder	2	3	11	1–21	5	4–11	0	0	0	0	Antipsychotic, 50%
Cocaine delusional disorder	1	2	4	—	18	—	0	0	1	100	Antipsychotic, benzodiazepine, methadone, tricyclic
Cocaine intoxication	1	2	1	—	37	—	0	0	1	100	None
Adjustment disorder with disturbance of emotion and conduct	2	3	6	0–12	7.5	7–8	2	100	2	100	Antipsychotic, 50%; benzodiazepine, 100%

[a] All 18 patients had moderate to severe dementia.

courses that were essentially the same. The most noteworthy aspect of these patients' treatment is that despite the despair they experienced before admission—all but one were suicidal—after a brief period each patient had achieved significant improvement in mood and had regained some hope and ability to establish goals. This was clearly brought about by a spectrum of psychosocial interventions: hospitalization itself, supportive psychotherapy, staff members' particular sensitivity to AIDS-related issues, and their active patient advocacy, including help in constructing combined financial and emotional support systems outside the hospital. Although four of the patients assigned a diagnosis of major depression accepted antidepressant medication, their clinical improvement clearly occurred in less time than is usually required for response to medication.

All of the patients in this series who were assigned a diagnosis of dementia had dementia of at least moderate severity according to the *DSM-III-R* criteria. Patients for whom table 1 reports mild cognitive deficits evidenced some cognitive dysfunction, documented in clinicians' notes or on neuropsychological testing, in excess of that expected for the primary psychiatric diagnosis, but they did not meet the *DSM-III-R* criteria for dementia.

Although all 18 patients with diagnoses of dementia were clearly clinically demented, results from corroborating laboratory and radiographic studies were variable. On CT or MRI, 12 patients demonstrated abnormalities (atrophy and/or white matter lesions), four had normal results on these studies, and two had had no recent study. On lumbar puncture, five had a nonspecific abnormality (increased protein level and/or elevated WBC count), three had normal findings, and 10 had had no recent study. No patient had a reversible cause of dementia.

Several stressors appeared to yield the adjustment disorders and brief reactive psychoses. For the adjustment disorders, these included newly diagnosed HIV-related disease (60%, N=9), loss of a love relationship (33%, N=5), housing/financial crises (27%, N=4), and perception of progression of the HIV-related illness (13%, N=2); 33% (N=5) of the 15 patients with adjustment disorders reported more than one significant stress. All of them were suicidal, except for the two with adjustment disorder with disturbance of emotion and conduct, who were homicidal.

For the brief reactive psychoses, the stressors included newly diagnosed AIDS-related complex (N=1), a recent progression of the medical condition (N=2), loss of housing (N=2), and a vigorous alternative therapy program that included rebirthing and primal scream techniques (N=1).

Although a detailed account of responses to medication and side effects is beyond the scope of this report, it should be noted that the demented patients evidenced considerable intolerance of haloperidol; this was not the case for the other diagnostic groups. This medication was responsible for two cases of urinary retention (in patients who were not receiving simultaneous anticholinergic therapy) and six cases of severe extrapyramidal reactions (although these patients were taking antiparkinsonian medications) that necessitated drug discontinuation.

As described in some detail in another publication (9), the patients with dementia were far more difficult than the others to integrate into the ward milieu and provided unique challenges to personnel from all mental health disciplines. These patients failed to respond to behavior modification techniques due to memory failure, disinhibition, and mental inflexibility, they manifested socially unacceptable behaviors (e.g., incontinence), and they grew increasingly dependent and required basic care and management of medical problems.

The nondemented patients, with two exceptions, were able to be discharged and treated as outpatients. One patient with brief reactive psychosis was discharged to a short-term halfway house, and one with schizophrenia was transferred to another hospital for administrative reasons.

Hospital stays for dementia patients were protracted, but not because of secondary psychiatric problems (e.g., organic affective disorder), which generally subsided within 2 weeks of hospitalization. These individuals required placement in subacute-care facilities that were in short supply. Patients with marked dementia who were fully ambulatory were the most difficult, as they required 24-hour individual care. The more debilitated patients were able to be transferred to 24-hour skilled nursing facilities for hospice care. None of the 18 patients with dementia was discharged to outpatient status.

DISCUSSION

DSM-III-R stipulates that the diagnoses of major depression, bipolar disorder, schizophrenia, and brief reactive psychosis cannot be assigned if there is evidence that an organic process initiates and maintains the mental disorder. All the patients in this series clearly had an underlying organic process, i.e., HIV disease, so the organic etiology stipulation was waived to allow assignment of a diagnosis that most closely described each patient's psychiatric illness. Except for the patients with dementia, it was not possible to determine whether the cause of mental disorder in a given patient was 1) a direct biological or psychological result of HIV infection, 2) a concurrent, unrelated event, or 3) a combination of these. The fact that nearly 60% of the patients had their first psychiatric hospitalizations after the likely time of their HIV infection suggests that HIV disease played an important role in the development of their mental disorders.

In approaching the HIV patient with major psychiatric disturbance, the physician should first find and treat all organic abnormalities that can be treated. Once this is done, the remaining psychiatric symptoms should be treated with biological, psychological, and social measures.

The depressed patients clearly benefited from psychosocial interventions, of which hospitalization itself was probably the most powerful. It is noteworthy that these individuals improved significantly within days of admission, whether or not they received a diagnosis of major depression. Perhaps this is because none of the patients had major depression alone, but a combination of adjustment disorder (which is amenable to nonpharmacologic treatment) with superimposed vegetative symptoms (organic mood disorder?) that were manifestations of HIV infection. The findings should certainly not be interpreted to mean that there is no place for somatic treatment of depression in HIV-spectrum patients; clinicians have successfully used medications to treat depression in these patients (11–13). The results of this study underscore the importance of psychosocial interventions with this population. Clinicians must also recognize that patients with AIDS and AIDS-related complex can experience marked changes in hope and hopelessness over brief periods, so that suicide planning that occurs during emotional turmoil should be interrupted.

While psychiatrists await the development of drugs that will prevent or retard HIV dementia—early reports on psychostimulants (12, 13) and especially zidovudine (14, 15) are hopeful—they should cautiously but actively try to treat its ravages. In this series of patients, haloperidol was frequently cited as yielding untoward side effects. Further investigation is required to elucidate the best pharmacologic approaches to the treatment of agitation and psychosis in these patients.

Demented patients often remain on acute-level services longer than necessary because of inadequate facilities for subacute care. The development of such services will lessen the burden on acute-care hospitals and on the patients who are forced to stay in them.

This case series study had a number of important limitations. The charts provided very few clinical details. The lack of a second reviewer of the records means that the author's potential bias in reviewing his own work was not eliminated. Perhaps the most serious limitation was the absence of follow-up data. Only three of the 60 patients were readmitted to the unit after resolution of their index episodes, although many more may have later required psychiatric hospitalization and received it elsewhere. Prospective studies of neuropsychiatric illness in HIV-spectrum patients, including the examination of biological markers accompanying syndromes and the effects of psychoactive medications on these syndromes, will help us offer these patients more accurate diagnosis and treatment.

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Time Course of Antipsychotic Effects of Neuroleptic Drugs

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The authors reviewed relevant studies in an attempt to define the onset and time course of antipsychotic effects of neuroleptic drugs. After excluding open trials, studies of chronically psychotic patients, and studies not using a placebo or nonneuroleptic sedative as a control, they found only five reports suitable for analysis. Among these, the degree of patients' improvement during neuroleptic treatment was similar regardless of the duration of the study. Also, in studies comparing neuroleptics with sedatives, similar improvement was observed with both treatments. Although neuroleptic drugs have been used clinically for 35 years, the timing of their specific therapeutic effects remains unclear.
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The introduction in the early 1950s of medicines with antipsychotic properties revolutionized the practice and theory of psychiatry (1). The efficacy of neuroleptics in the treatment of psychoses, both functional and organic, has been established beyond doubt (1, 2). However, after more than 35 years of use of these drugs and research into their action, many basic issues concerning their clinical pharmacologic properties remain obscure (3). Among these uncertainties is the time course of patients' response to these agents (3).

Although there are many reports describing relationships between neuroleptic dose, route of administration, and the onset of antipsychotic effects, relatively few of these studies have been controlled (3). Since the symptoms of psychosis are variable, may respond to environmental factors, or may decrease or remit spontaneously (4), only controlled studies can provide interpretable data on the specific antipsychotic effects of neuroleptic drugs.

We reviewed controlled studies in an attempt to determine the onset and time course of the antipsychotic effects of neuroleptics. Knowledge of the course of such effects would be of potential value not only in establishing rational guidelines for clinical treatment but also in designing and interpreting studies on the pharmacologic actions of these drugs.

METHOD

We examined published studies of the efficacy of antipsychotic agents in controlled trials. Access to this large body of literature was facilitated by the use of two extensive bibliographies on the subject (5, 6) augmented by a computer-assisted literature search of the National Library of Medicine's MEDLINE file through 1986. This process yielded more than 1,300 citations.

We selected for further review reports in which patients with acute psychotic episodes or acute exacerbation of chronic psychosis were randomly assigned to treatment with a neuroleptic and either an inactive placebo or a nonneuroleptic sedative. Most studies were open trials and therefore were excluded from analysis. We excluded 18 studies in which antipsychotic agents were administered to stable, chronically ill patients, because there are inherent difficulties in rating the degree of improvement of such patients and because many such patients respond only minimally to treatment (1). Also, we excluded studies comparing the efficacy of two or more different neuroleptic regimens unless a placebo or a sedative was used as a control, because such designs do not allow the separation of nonspecific (e.g., spontaneous, placebo, or sedative) and specific (antipsychotic) effects. By applying these criteria, we excluded a number of important studies from our analysis. For example, three National Institute of Mental Health Psychopharmacology Research Branch Collaborative Study Group reports (7–9), which were designed to assess the efficacy of antipsychotic drugs (7), identify predictors of response (9), and compare treatment with high and low doses (8), were not included because of the absence of time course data. These important studies did, however, document the superiority of antipsychotic drugs over sedatives and placebo after 6 weeks of treatment (7, 9). Other important studies by Casey et al. (10, 11) were excluded

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TABLE 1. Data From Five Controlled Studies of Time Course of Neuroleptic Effects in Acutely Psychotic Patients

Study	N	Diagnosis	Treatment	Mean Neuroleptic Dose (mg/day)	Outcome Measure	Length of Treatment (days)
Abse et al. (16)	30	Acute psychosis	Chlorpromazine, opium, or placebo	Chlorpromazine, 329 p.o.	Nurses' ratings of ward behavior	21
Reschke (17)	50	Acute psychosis	Haloperidol, chlorpromazine, or placebo	Haloperidol, 8.7 i.m.; chlorpromazine, 100 i.m.	Target symptom severity scale	0.08
Schooler et al. (18)	24	Acute schizophrenia (RDC)	Chlorpromazine or placebo	Chlorpromazine, 900 p.o.	Psychiatrist's global severity rating	21
Johnstone et al. (19)	45	Acute schizophrenia (Present State Examination)	α-flupenthixol, β-flupenthixol, or placebo (and chlorpromazine as needed)	α-flupenthixol, 8 p.o.; β-flupenthixol, 8 p.o.	Rating scale for schizophrenia	28
Lerner et al. (20)	40	Acute psychosis	Haloperidol or diazepam	Haloperidol, 27.5 i.v. and p.o.	Brief Psychiatric Rating Scale	1

because chronically psychotic patients constituted the majority of the study samples. Finally, the important long-term, multimodality treatment outcome studies of May et al. (12, 13) and Hogarty et al. (14, 15) were excluded because of the lack of time course data and because a majority of the patients studied were chronically psychotic. This exclusion process left only five reports (16–20) that provided sufficient information regarding time course of antipsychotic effect to permit analysis.

Although several studies had used similar psychometric scales for rating symptomatic improvement and outcome, time course data had been assessed by different instruments in each study. Therefore, to permit standardized comparisons, we converted measures of response to percentage reductions in symptom severity, with the severity scores recorded immediately before initiation of treatment uniformly set at 100%.

RESULTS

The five controlled studies (16–20) describing the time course of antipsychotic effects in acutely psychotic patients spanned an interval from 1960 (16) to 1979 (20). They were heterogeneous in subject samples, cohort sizes, specification of diagnostic criteria, study intervals, and neuroleptic and control agents studied. Abse et al. (16) studied 30 patients exhibiting acute "excessive tension, anxiety or emotional disturbance causing severe personal discomfort or difficulties in word management." Patients were randomly assigned to treatment with chlorpromazine, 600 mg/day for 2 days, then 300 mg/day (N=7), powdered opium (N=7), or placebo (N=10)—dropouts were not accounted for—for a 21-day trial. Ratings were made on the MMPI, an anxiety checklist, and a scale for nurses' ratings of ward behavior. Reschke (17) studied 50 "severely agitated schizophrenic patients" (further criteria not specified) randomly assigned to treatment with haloperidol, 1, 2, or 5 mg i.m. every 30 minutes (N=29), chlorpromazine, 25 mg i.m. over 30 minutes (N=10), or placebo (N=11) over a 2-hour interval. A target symptom scale and the Brief Psychiatric Rating Scale (BPRS) were used to rate response. Schooler et al. (18) reported on 24 patients meeting the Research Diagnostic Criteria (RDC) for schizophrenia who were "at least 'moderately ill' on a 7-point scale of severity after a 1-week placebo washout period." Subjects were randomly assigned to chlorpromazine, increased to 1000 mg/day after 7 days (N=24), or placebo (N=9) for a total treatment period of 28 days. Clinical assessment included the Inpatient Multidimensional Psychiatric Scale, the Clinical Global Impression (CGI), the Nurses' Observation Scale for Inpatient Evaluation, and global severity ratings. In the fourth study, Johnstone et al. (19) studied the response of 45 patients with acute schizophrenia, defined by the Present State Examination (PSE), to α-flupenthixol, up to 9 mg/day (N=15), β-flupenthixol, up to 9 mg/day (N=15), or placebo (N=15). Response was measured over a period of 4 weeks by the Krawiecka rating scale for schizophrenia. Finally, Lerner et al. (20) studied 40 newly admitted, acutely psychotic patients (heterogeneous diagnoses) randomly assigned to treatment with haloperidol, 20–35 mg i.v. or p.o. (N=20), or diazepam, 30–40 mg i.v. (N=20), received over a period of 24 hours. Ratings were done using the BPRS and the CGI.

One study (17) examined improvement during the first 2 hours of acute treatment, one (20) measured improvement after 1 day, and three studies followed improvement at 3-day intervals (16) or weekly (18, 19) over 3–4 weeks (table 1).

The reported time courses of improvement are shown in figures 1 and 2. Figure 1 represents a compilation of the studies of neuroleptic versus placebo; figure 2 represents the studies of neuroleptic versus an active control drug.

The same overall degree of improvement was observed during treatment with all the agents tested within each of the markedly different time intervals studied. Furthermore, when a neuroleptic was com-

FIGURE 1. Time Course of Symptom Reduction in Acutely Psychotic Patients in Four Studies Who Were Given Neuroleptics or Placebo

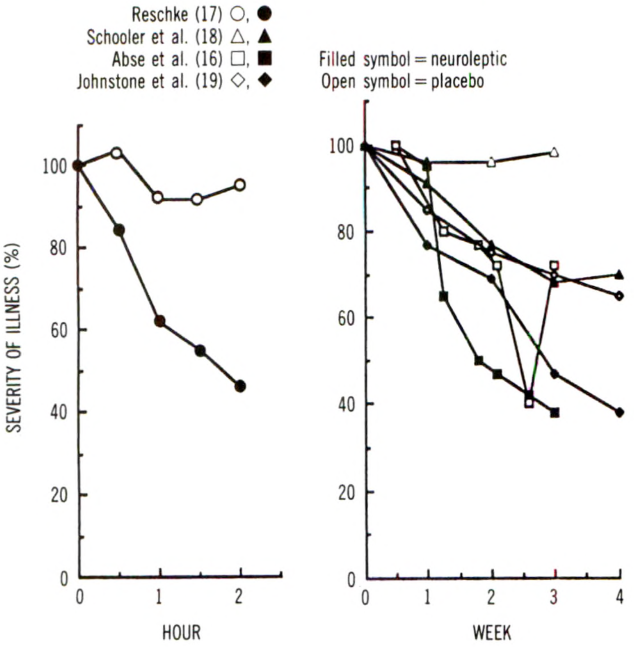
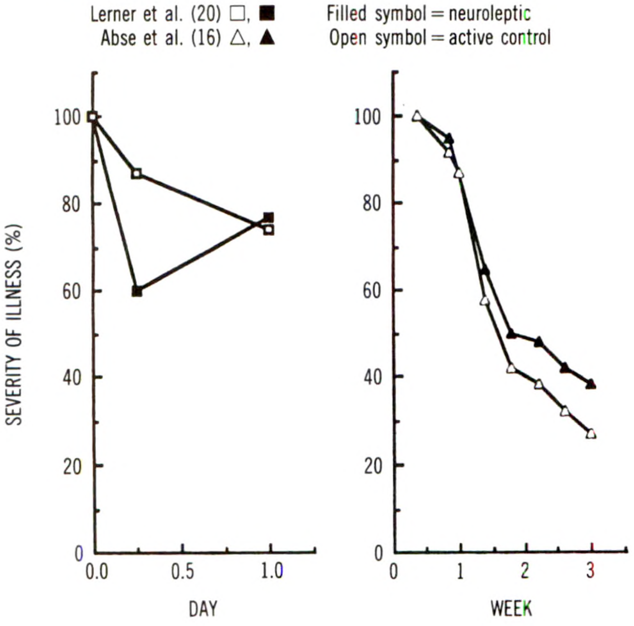


FIGURE 2. Time Course of Symptom Reduction in Acutely Psychotic Patients in Two Studies Who Were Given Neuroleptics or Active Control Drugs



pared to a sedative—diazepam (2) or opium powder (16)—the sedative demonstrated efficacy similar to that of the neuroleptic during the first day (16, 20) and through 4 weeks (20) of treatment.

DISCUSSION

It is striking that in an extensive literature search, we found only five controlled studies which yielded informative data on the onset of the antipsychotic effects of neuroleptic drugs in patients suffering acute episodes or acute exacerbation of psychosis. It is also interesting that in studies ranging in length from hours (17) to weeks (16, 18, 19), the degrees of overall response observed in the patients were quite similar. That is, short studies observed moderate improvement within hours or days, but longer studies observed little improvement in the first few days and marked improvement only over weeks of treatment. Finally, it is notable that in studies in which neuroleptics were compared to active nonneuroleptic sedative agents (16, 20), both treatments produced similar symptomatic improvement in the first days, and perhaps weeks, of treatment.

The proper interpretation of these findings is not clear. Perhaps the early effects of antipsychotic drugs are nonspecific and are largely the same as those of sedative agents. The success of placebo treatment suggests that early improvement may be largely due to the nonspecific effects of hospitalization or other clinical interventions apart from the specific therapeutic effects of prescribed pharmacologic agents (3, 20). Alternatively, it is possible that standard ratings of psychosis do not provide a reliable measure of specific antipsychotic responses. In particular, they may be heavily influenced by expectations of both observers and patients about the course of response, as suggested by the correlation we observed between the predetermined length of the studies cited and the rate at which patients were reported to improve. In that case, little can be gained by studies, such as those reviewed here, not designed to be blind with respect to time.

There are, of course, other limitations to the comparability and interpretation of the studies we examined. First, since each study used a different psychometric rating scale, it is possible that the similarity in improvement observed over widely dissimilar time intervals was an artifact of the variability in rating methods or of a tendency for ratings to regress to lower mean values in repeated assessment, regardless of the duration of a study (21). However, it seems unlikely that the substantial apparent improvement recorded on one scale within hours of treatment would not be observable on other scales if ratings reliably reflect clinical state.

Second, these findings might be attributable to differences between studies in neuroleptic dosage or route of administration. However, neuroleptics were administered at doses widely considered to be within the range for producing maximal therapeutic effects (22).

Finally, the wide variability in time course of response that we found in these studies might reflect differences in the composition of the subject samples. Since diagnostic criteria were specified in only two studies (18, 19), this possibility could not be assessed.

Whatever the limitations of the available studies, one striking conclusion remains: there appears to be no body of controlled studies with replicable results that provides convincing documentation of the onset and characteristic time course of the antipsychotic effects of neuroleptic drugs given to patients with acute exacerbations or acute onset of psychosis. Rather, available studies are few and yield conflicting data on this subject. It is interesting that little is known about this same variable in stable, chronically psychotic patients as well (1). Thus, the main conclusion from the limited data available is that the timing and rate of development of the specific therapeutic effects of neuroleptics remain uncertain. Since this information has considerable importance in planning clinically optimal and cost-effective treatment of psychotic patients, new, well-controlled studies—especially studies with ratings performed blind to or controlling for the duration of treatment—would be worthwhile.

These findings also suggest the need for further studies designed to compare the acute response to treatment with neuroleptics and the response to treatment with nonneuroleptic sedative agents. Such studies would be particularly valuable if comparable short-term results are achieved, suggesting that lower doses of neuroleptic agents augmented by sedative agents may effectively manage acute psychosis while reducing the risk of neuroleptic-related side effects. Finally, further controlled studies designed to assess the time course and onset of antipsychotic effects would be well-suited to address the relationship between rapidity of response and long-term outcome (23).

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Defining and Measuring Stabilization of Patients During 4 Years of Intensive Community Support

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The first 4 years of an intensive community support program were evaluated in terms of key variables of patient stabilization. Patients (N=196) had previously demonstrated an inability to manage themselves without repeated and/or lengthy hospitalizations. During program participation, there were significant reductions in hospital days and events (80%), jail incarcerations and charges, billings per patient, and stressful events. Patients reported increased satisfaction both with their lives and the program. The results support the value of continued multidimensional and multimethod examinations of patient stabilization.

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Community support programs have emerged as vital components of treatment for the chronic mentally ill facing fragmented and inadequate care after deinstitutionalization (1, 2). Test and Stein (3) and Braun et al. (4) analyzed approximately 60 controlled studies and suggested that when experimental community treatment was compared to traditional hospitalization, observed differences tended to favor community treatment by "reducing hospital readmission and, in a number of instances, increasing independent functioning" (4).

It is becoming clear that emphasis on hospitalization alone is an inadequate measure of outcome (5, 6). If reduced hospitalization is not accompanied by stabilization in other respects, the benefits of community support may be questioned. Another measure of outcome is improved quality of life (7, 8). The data on this point have been mixed. Franklin et al. (9) found that case management increased hospitalization and did not have a substantial impact on the quality of life during a 12-month period. Another study of 82 patients in a rehabilitation-oriented case management program (10) found hospitalization rates were not reduced, but quality of life improved with respect to occupational functioning, social isolation, and more independent living.

Studies published to date have remained focused on broad classification of outcome, with little examination of relationships among the variables measured, making interpretation of programmatic success deceptively simple. The present study examined the first 4 years of service offered by an urban community support program, which served severely disabled patients with few family ties and multiple hospitalizations. The goal was to extend prior research by examining aspects of stabilization including hospitalization and jail patterns, internal billing, patient stabilization and distress events, patient satisfaction, and terminations. By correlating these patterns and their interactions, we expected that a more thorough understanding of the effect of case management on patient stabilization and satisfaction could be achieved. In addition, there were six specific hypotheses, three of which related to hospitalization patterns: 1) Hospital days and episodes will decrease by 80% by the end of the first program year; 2) a decrease by 80% in hospital days and episodes will be maintained by the end of the second year; 3) decreased hospitalization will not be accompanied by increased jail time; 4) billing will decrease from year 1 to year 2 and then remain fairly stable; 5) stabilization will improve over time as measured by a reduction in daily distress events; and 6) patients' satisfaction will be correlated with global improvement in their lives, satisfaction with community support program services and living arrangements, and less objection to taking medication.

METHOD

Patients

The present study summarizes the first 4 years of the community support program at Harborview Community Mental Health Center in Seattle. A total of 196 patients participated, with a mean±SD enrollment of 26.8±16.4 months (range, 1.0–50.7 months). Most of the patients were men (N=123, 62.8%), young (mean ±SD=34.3±9.8 years), Caucasian (N=108, 55.1%),

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and schizophrenic. For analyses, diagnostic groups were dichotomized into schizophrenia (schizophrenic, schizoaffective, and paranoid disorders) (N=147, 75%) and major affective disorder (N=49, 25%). Most of the patients (N=119, 60.7%) had never married; only a small minority (N=6, 3.1%) were married. Thirty-five percent (N=68) had some college; almost half (N=95) had no drug or alcohol involvement; the mean monthly income was $343.13; and the mean group Global Assessment Score was 32.6±7.4.

Measurements

Hospitalization. Psychiatric hospitalizations were documented for the 24 months before each patient's admission, as well as during enrollment in the community support program. A hospital event was classified according to voluntary or involuntary legal status. If the patient's legal status changed, a new event was recorded. Hospital days and events during enrollment in the community support program were totaled in 6-month increments. If an event extended between 6-month periods, the event was recorded for each period. For comparison, data for the period before enrollment in the community support program were divided by four (semiannualized), and each patient was used as his or her own control.

Jail incarcerations. The community support program collected data locally from the King County Jail on patients in the program in 1986 who would sign a consent form and were considered to have reliable data (N=91). The information included the admit and discharge dates for each jail incarceration and the charges. Jail data, like hospitalization data, were collected 24 months before admission and at 6-month intervals during enrollment in the community support program. For analysis, charges were grouped into nine categories: theft, trespassing, property destruction, assault, other crimes against persons, weapons offenses, forgery/fraud, drug/alcohol, and other miscellaneous charges.

CSP billing charges. Monthly community support program billing charges were collected from 183 patients (13 patients were billed through another agency). The billing charge was zero for patients when they were hospitalized. For the current analysis, monthly billing was summed to obtain annual charges per patient per year in the community support program.

Patient Monitoring Form. The Patient Monitoring Form was a daily checklist completed by case managers for each patient. It consisted of 17 patient stress event categories and five patient service receipt categories. Monthly totals were calculated for each category, and the 17 stress events were summed to obtain a stress event total. This paper addresses the categories of residential change, noncompliance with medication, substance abuse, suicide threats, suicide attempts, arrested/jailed, and the stress event total. A list of additional categories is available from the authors.

The Patient Monitoring Form was introduced 2 years after the program started; data were available for 151 of the 196 patients. This measure replaced available functional scales, which inadequately reflected change for these patients.

Patient Satisfaction Survey. The Patient Satisfaction Survey was a six-question self-report form used to assess how patients felt about several areas of their lives and community support program services. Questions either used a 5-point Likert scale or were multiple choice.

Program Description

The criteria for admission to the community support program were as follows: at least 18 years of age; diagnosis of schizophrenia, major affective disorder, or paranoid disorder; in the prior 2 years, at least three psychiatric hospitalizations, three jail psychiatric ward detentions, a combination of three jail-hospital detentions, or one 6-month psychiatric hospitalization; repeated failure of involvement in outpatient treatment; and residence in downtown Seattle. The program maintained approximately 120 patients at a time, with individual caseloads of 10 or 11 patients. It was based on the program described by Stein and Test (11), which emphasized assertive case management and outreach by a multidisciplinary staff, improving daily living skills and coping strengths, and crisis intervention. In that program, as in this community support program, there was a focus on reduced need for hospitalization, increased patient stabilization, and improved quality of life. Frequent outreach was a key component of case management services. Other program elements included psychiatric services, 24-hour crisis intervention, medication management, alternative (respite) beds, temporary emergency housing, and financial management including a protective payee system (case manager) responsible for paying for basic needs and distributing discretionary income.

RESULTS

Hospitalization Patterns

As hypothesis 1 predicted, hospitalization days decreased by 80% by the end of year 1 in the program. In the 2 years before the community support program, patients were hospitalized a mean of 33 days per 6-month period. After 1 year of the program, mean hospitalization was 6 days, a significant reduction of 81% ($t=8.71$, $df=148$, $p<0.0001$). Once patients were in the program, there were no further statistically significant decreases, in spite of an apparent one (see table 1).

Hospital events also decreased dramatically—71% by year 1 and 79% by year 2—just under the 80% reduction predicted by hypothesis 2. The year 1 decrease was significant ($t=13.42$, $df=148$, $p<0.0001$,

TABLE 1. Hospital Events and Length of Stay for Psychiatric Patients in a Community Support Program

		Events			Length of Stay (days)			Patients With No Hospitalization	
Item	N	Mean	SD	Percent Reduction[a]	Mean	SD	Percent Reduction[a]	N	%
Before program (semiannual)	191	1.1	0.6	—	32.7	30.1	—	—	—
During program									
6 months	179	0.4	0.7	67	8.8	24.1	72	130	73
12 months	150	0.3	0.7	71	6.0	21.8	81	117	78
18 months	123	0.3	0.7	77	7.5	27.7	76	102	83
24 months	103	0.2	0.6	79	5.5	22.5	83	86	84
30 months	85	0.2	0.6	84	4.3	15.0	87	76	89
36 months	71	0.3	0.8	78	3.8	11.4	88	61	86
42 months	60	0.2	0.5	81	5.9	17.7	80	48	80
48 months	35	0.1	0.4	89	2.5	9.4	90	31	89

[a] Calculated by comparing each community support program period with pre-program figures, with each patient as his or her own control.

two-tailed test), although later decreases were not significant from each other.

Particularly noteworthy is the percentage of patients *never* rehospitalized. Between 72% and 89%, depending on the year measured, were not hospitalized in a given year. Over the 4 years, 50% of the patients were never hospitalized.

In order to differentiate those who were likely to be hospitalized while in the community support program, we used a discriminant analysis to examine several variables expected to predict inclusion in one of two groups: patients never hospitalized and patients hospitalized two or more times. Only patients in the community support program more than 1 year were used in the analysis ($N=122$). Variables tested in the discriminant analysis were age, sex, diagnosis, number of hospital events (voluntary and involuntary) before entering the community support program, race (white/nonwhite), substance abuse, and protective payee status. The patients who were hospitalized while in the community support program were differentiated from those who were not by the following variables: more pre-program involuntary (Wilks's $\lambda=0.92$, standardized canonical $r=0.69$) and voluntary ($\lambda=0.85$, $r=0.32$) hospital events, younger age ($\lambda=0.88$, $r=-0.49$), affective disorder diagnosis ($\lambda=0.84$, $r=0.27$), and substance abuse ($\lambda=0.86$, $r=0.32$) (all lambda values significant at $p<0.003$). Although 71% of the cases were correctly classified, cross-validation was not possible on this small sample. Thus, these results should be viewed as descriptive rather than inferential.

Jail Patterns

A frequent concern is that decreased hospitalizations for psychiatric patients will be complemented by increased jail episodes. Overall, this was not borne out by the present data, thus partially confirming hypothesis 3. Preliminary analyses examined demographics between patients for whom we were able ($N=91$) and were not able ($N=105$) to secure jail data. Few differences were found. The group for whom we were able to document jail data (whether or not they had a jail record) included clients with both more voluntary hospitalizations before the program ($t=1.99$, $df=189$, $p=0.048$, two-tailed test) and more involuntary hospital days during the program ($t=2.22$, $df=194$, $p=0.028$, two-tailed test). In addition, those for whom jail data were available were more likely (76% [$N=69$] versus 24% [$N=22$]) to have protective payee status ($\chi^2=13.18$, $df=1$, $p=0.0003$). Therefore, the jail data are somewhat biased, relative to the overall community support program, in the direction of patients who were more likely to need external controls to maintain a level of community functioning.

A high percentage of patients (40.7%, $N=37$) were jailed during the 2 years before they entered the community support program. In the community support program, there were significant decreases in the mean number of jail events per year (35% reduction—from 0.54 to 0.35; $t=2.04$, $df=90$, $p<0.05$, two-tailed test) and number of jail charges per year (39% reduction—from 0.82 to 0.50; $t=2.24$, $df=90$, $p<0.05$, two-tailed test); however, mean jail days per year did not change. Another perspective on these data is the percentage of patients with no jail time in their records. Before the community support program, 59% ($N=54$) of the patients had no jail time. After 6 months of the program this category increased to 85% ($N=77$); it remained at this level, ±6%, during the 4 years. These latter figures describe annual jail time for the group in treatment, not individuals.

The patients' jail experience before the program could somewhat predict their jail patterns while in the community support program; the mean number of jail events ($r=0.53$, $df=89$, $p<0.001$), mean number of days in jail ($r=0.43$, $df=89$, $p<0.001$), and mean number of charges ($r=0.62$, $df=89$, $p<0.001$) were significantly correlated across the two time periods.

Regarding hospital and jail relationships before the patients entered the community support program, only jail events and hospital events were significantly negatively correlated ($r=-0.18$, $df=89$, $p=0.05$). No correlations were significant between these classes of variables after entry into the community support program.

Billing Patterns

In order to incorporate annual increases in charges, all billings were converted to 1986 dollars. Supporting and extending hypothesis 4, charges showed a general decrease in billing per patient over the 4 years, from a mean of \$4,240±\$2,230 in year 1 to \$3,552±\$1,912 in year 4. Charges between years 1 and 2 significantly decreased (t=6.12, df=96, p<0.001), as did charges between years 1 and 3 (t=5.19, df=65, p<0.001) and between years 1 and 4 (t=4.35, df=36, p<0.001, two-tailed tests in all three cases). A longitudinal perspective is available by examining the group (N=37) in the community support program for all 4 years: year 1=\$5,096±\$2,609, year 2=\$3,642±\$1,710, year 3=\$3,157±\$1,460, and year 4=\$3,552±\$1,912.

Billings were also examined according to demographic patterns. The high billing group, those above the median billing figure, was made up of significantly more protective payee patients (56%–64%) than nonpayee patients (16%–32%) across all 4 years. In year 2 significantly more high billing group members were white (62%) than nonwhite (36%) (χ^2=5.47, df=1, p=0.02), a finding that was repeated, nonsignificantly, during years 1 and 3. Finally, significantly more schizophrenic (56%–60%) than major affective disorder (28%–32%) patients were in the high billing group during 3 of the 4 years.

Patient Stabilization and Distress Events

The daily Patient Monitoring Forms provided a way of tracking specific aspects of patients' lives. Because the Patient Monitoring Forms were developed after the initiation of the program, they do not provide adequate data about patient change. Rather, the distress events provide a description of the relative frequency of different events and number of patients involved. Overall during the program, the rank order of distress events and the number of events per patient per month were as follows: medication noncompliance (1.43), substance abuse (1.24), arrests (0.55), residential change (0.09), suicide threats (0.06), and suicide attempts (0.01).

In support of hypothesis 5, total distress events were significantly correlated with months in the program (r=−0.74, df=42, p<0.001); the longer a patient remained in the program, fewer distress events occurred. Total distress was not correlated with billings.

Patient Satisfaction

As a group, the patients were very positive about several aspects of their lives while in the program. Ninety-three of the 196 patients filled out the Patient Satisfaction Survey. Comparisons between those who did and did not complete the survey indicated that those who completed it were more likely to have protective payee status (χ^2=8.81, df=1, p=0.003), have fewer involuntary hospitalizations during the program (t=3.40, df=194, p=0.001, two-tailed test), and have fewer hospitalization days (t=3.29, df=194, p=0.001, two-tailed test). There were no demographic or diagnostic differences.

The majority of the patients (78.5%) evaluated their lives as being somewhat or much better since they entered the program, and 73% rated the community support program services as good, very good, or excellent. In addition, 65%–70% were satisfied with their current residential situation, were satisfied about their recent contact with other (nonprogram staff) people, agreed that taking prescribed medications was necessary and important to them, and agreed that help was available from the program when they needed it (see table 2).

TABLE 2. Responses to Patient Satisfaction Survey by 93 Patients in a Community Support Program

Item	N	%
Overall, my life since I entered the community support program is:		
Much worse	5	5.4
Somewhat worse	7	7.5
Unchanged	8	8.6
Somewhat better	44	47.3
Much better	29	31.2
During the past month my living (residential) situation has been:		
Very unsatisfactory	7	7.5
Moderately unsatisfactory	7	7.5
Slightly unsatisfactory/satisfactory	18	19.4
Moderately satisfactory	30	32.3
Very satisfactory	31	33.3
During the past month my contact with other people (except community support staff) has been:		
Very unsatisfactory	5	5.4
Moderately unsatisfactory	4	4.3
Slightly unsatisfactory/satisfactory	24	25.8
Moderately satisfactory	34	36.6
Very satisfactory	26	28.0
Taking prescribed medication seems necessary and important to me.		
Strongly disagree	16	17.2
Moderately disagree	6	6.5
Slightly disagree/agree	12	12.9
Moderately agree	12	12.9
Strongly agree	47	50.5
Help is available from the community support program when I need it.		
Strongly disagree	8	8.6
Moderately disagree	9	9.7
Slightly disagree/agree	12	12.9
Moderately agree	34	36.6
Strongly agree	30	32.3
How would you rate the quality of services you have received from the community support program?		
Excellent	19	20.4
Very good	22	23.7
Good	27	29.0
Fair	17	18.3
Poor	8	8.6

Hypothesis 6 was only partially supported. A stepwise multiple regression examined the variables contributing to the degree of general life satisfaction since the patients entered the program. Variables entered into the equation were satisfactory contact with people (excluding program staff) in the past month, high rating of program services, and satisfaction with residential situation in the past month. The need for medication and availability of help from the program did not enter the equation. The equation was significant ($F=16.38$, $df=3, 89$, $p<0.001$; $R^2=0.36$).

A further set of analyses was conducted to determine whether patient satisfaction was differentiated by key demographic and clinical variables. There were some sex differences: Women were more likely to have satisfactory contacts with others (Mann Whitney $U=774.0$, $p=0.04$), agree that taking prescribed medications was necessary ($U=790.5$, $p=0.05$), and rate the program services as of better quality ($U=720.0$, $p=0.01$). There were racial differences: Blacks were more likely to agree that medications were necessary and important to them than were whites ($U=598.0$, $p=0.02$) and were also more satisfied with their contacts with other people in the last month ($U=621.5$, $p=0.04$). Those with two or more hospitalizations rated their life in the program as worse than did those with no hospitalizations ($U=442.0$, $p=0.004$). Age was modestly correlated with satisfactory contact with others ($tau=0.15$, $p=0.03$) and with the opinion that medications were necessary and important ($tau=0.15$, $p=0.03$).

Discharge/Termination Patterns

Of 196 patients admitted to the community support program, 76 (38%) were terminated over the 4 years. Terminated patients were in the program a mean±SD of 17.5±10.7 months (range, 1.6–47.2 months). The two most common reasons for termination were that the patient moved from the area (N=22) or experienced a long-term commitment (more than 3 months) to a psychiatric or correctional facility (N=18). Fifteen patients refused to participate in the program; eight transferred with their case manager when he transferred to another agency; four disappeared; four died (two by suicide); three were determined to no longer need the program and were discharged to the medication clinic; one, because of his antisocial behavior and drug use, was terminated as being untreatable; and one was discharged after she assaulted her case manager.

Discharge patterns were further examined to determine whether, during each year, patients who were discharged differed on demographic and patient variables from patients who remained in the program. The first comparisons were between patients who left in their first year (N=30) and patients who remained beyond the first year (N=147). There were no demographic differences between these two groups; only hospital rates differed. Those discharged had significantly more involuntary hospital events (1.3 versus 0.4; $t=5.15$, $df=175$, $p<0.001$), significantly more involuntary hospital days (67.9 versus 12.8; $t=5.28$, $df=175$, $p<0.001$), and significantly more voluntary hospital events (0.46 versus 0.13; $t=2.52$, $df=175$, $p=0.012$, two-tailed tests in all three cases).

A similar pattern was found in a comparison of those who left versus those who stayed through year 2 and year 3 (data are available from the authors). No differences were found between those who left versus those who remained through their fourth year.

DISCUSSION

These results describe several components of stabilization in addition to the significant reduction in hospital days and events after the first year of the community support program. Such reduction, confirmed in hypotheses 1 and 2, is consistent with much of the literature on community support programs regarding reduction of hospitalization (3, 4), but it also demonstrates this in a population selected for high hospital recidivism. Goering et al. (10) have suggested that an urban program's failure to affect hospitalization rates may have come from a lack of emphasis on crisis intervention, lack of alternative acute care, and lack of case manager control of care during relapses. These issues were addressed in the structure of the present program.

The ability to predict higher risk for hospitalization during intensive community support is of considerable clinical value. The discrimination of 51 patients with two or more hospitalizations during the program identified variables (voluntary and involuntary hospital events before the program, younger age, affective disorder, and substance abuse) that may merit attention when efforts are made to prevent relapse and rehospitalization.

Confirming hypothesis 3, jail events per year and jail charges per year decreased significantly in spite of the fact that this program maintained a philosophy similar to that of Test and Stein's program (11) of making patients responsible for their violations of the law. Billing data (hypothesis 4) decreased in charges per patient over 4 years, but some patients required more frequent contact (higher billing) in order to remain stable. It is interesting that the variables describing the higher billing group—schizophrenia and protective payee status—did not describe the higher hospitalization group mentioned earlier.

Confirming hypothesis 5, there was a significant negative correlation between stress events and months in the program (another aspect of stabilization). These events were stressful for both case manager and patient. Recording stress events on the daily Patient Monitoring Form reminded case managers that certain negative events required increased attention and/or revised treatment plans.

Although this program began with the intent of treating most patients indefinitely, a policy evolved of discharging patients who were not in the community for 90 days in order to replace them with newly referred patients. An average of 1.5 patients per month were discharged, about half of whom (52%) either left the area or were in a hospital or correctional facility. In addition, the patient mobility that contributed to termination was greater than anticipated and interrupted continuity of care. Relating to hypothesis 6, patients who remained in the program were very positive about quality of their life and the program's services. This contrasted with the study by Franklin et al. (9), who found that such programs had little effect on the quality of life.

In summary, decreased jail contact, decreased billing, fewer stress events, and improved self-reported quality of life provide a broader concept of stabilization than do hospitalization data alone. Our findings support prior critiques of an exclusive focus on the latter outcome measure (5, 6).

Data interpretation requires several reservations. Not all measures were available on all patients across 4 years, and this necessitated comparative pretests between subgroups as well as testing by year in the program where appropriate. The results do not reveal a patient or program "norm" but rather suggest several longitudinal and cross-sectional patterns associated with patient stabilization in an urban-based intensive community support program. A program structured to follow most patients indefinitely, even after termination, would partially address this limitation. Such an approach is difficult without a commitment to continuity provided by patient tracking systems. As such systems become more developed, needed additional studies of patient stabilization will be possible.

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Panic Disorder and the Menstrual Cycle: Panic Disorder Patients, Healthy Control Subjects, and Patients With Premenstrual Syndrome

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The authors prospectively evaluated 20 normally menstruating women with panic disorder across a minimum of two drug-free menstrual cycles. There were no significant effects of menstrual cycle phase on anxiety ratings in the panic disorder patients or in 20 healthy control subjects; this contrasted with a robust increase in premenstrual anxiety in 20 subjects with premenstrual syndrome. These findings suggest that the symptoms of panic disorder are not commonly exacerbated by the premenstrual phase of the menstrual cycle and highlight the need for prospective evaluation in the attempt to document an association between psychiatric symptoms and the menstrual cycle.

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The effect of the menstrual cycle on various medical and psychiatric syndromes has become a topic of considerable interest (1). The premenstrual phase of the menstrual cycle has been associated with the exacerbation of medical illnesses such as epilepsy (2) and asthma (3). Similarly, psychiatric disorders have also been reported to worsen premenstrually. For example, some women with bipolar illness or schizophrenia have a premenstrual recurrence or exacerbation of symptoms (4–8). Suicide attempts and psychiatric admissions have been reported to be disproportionately high during the premenstrual phase (9, 10). A premenstrual increase in the frequency of binge eating in bulimia was observed in one study (11), although another study failed to demonstrate such a relationship (12).

Despite this considerable literature describing an effect of the menstrual cycle on concurrent psychopathology, little is known about the relationship between menstrual cycle phase and the symptoms of panic disorder, a syndrome that afflicts predominately women (13). In a survey of 41 women with panic disorder, 63% complained of premenstrual worsening of their symptoms (i.e., anxiety, panic attacks, avoidance) (M.B. Stein and T.W. Uhde, unpublished observations). Breier and colleagues (14) reported that 51% of female agoraphobics experienced premenstrual exacerbation of anxiety symptoms. These estimations relied, however, solely on patients' retrospective assessment of the relationship between their symptoms and menstrual cycle timing, a methodology subject to both inaccurate recall and selective information processing biases (15–18). More recently, in a study of 10 women with panic disorder, Cameron and associates (19) reported that despite patients' retrospective reporting of premenstrual worsening, this was generally not confirmed on prospective assessment.

In the present study, we describe the results of a prospective assessment of the relationship between panic disorder and the menstrual cycle in 20 women with panic disorder (with or without agoraphobia). Ratings were obtained during at least two menstrual cycles in which all subjects were medication free and consisted of daily self-report ratings of anxiety (Spielberger State-Trait Anxiety Inventory, State Form [20], and visual analogue scales) and panic attacks. We compared the symptom ratings to those of 20 healthy female control subjects and 20 women with premenstrual syndrome (PMS). To our knowledge, our findings represent the largest prospective, controlled report in the literature of the relationship between panic disorder and the menstrual cycle.

METHOD

Subjects

The panic disorder patients consisted of 20 women who participated in ongoing studies in the Section on Anxiety and Affective Disorders at the National Institute of Mental Health (NIMH). All patients were diagnosed by a research psychiatrist who used the Sched-

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ule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (21), modified by us for use in anxiety disorders. All panic disorder patients met the Research Diagnostic Criteria (RDC) (22) for agoraphobia and/or panic disorder, and none met concurrent criteria for an affective disorder. All patients were determined to be medically healthy on the basis of a complete physical examination, ECG, CBC, SMA-20 biochemical panel, thyroid indices, and urinalysis. Women with panic disorder were included in this study if they reported regular menstrual cycle lengths (21–35 days) and they had completed ratings for at least two menstrual cycles while drug free. The mean±SD age of the patients with panic disorder was 34.1±7.0 years.

The healthy control group consisted of 20 medication-free, normally menstruating women who were recruited as paid volunteers through the National Institutes of Health volunteer office. Their mean age was 33.2±7.1 years. All healthy control subjects received the same medical and psychiatric screening as the patients, and they were determined to be free of current medical or psychiatric illness, the latter determined by administration of a modified SADS-L interview.

The PMS patients consisted of 20 women participating in studies at the NIMH premenstrual syndrome clinic. Their mean age was 36.0±5.9 years. The timing of their mood symptoms was prospectively confirmed with daily self-ratings, as previously described (23); for at least two of three menstrual cycles, they had a 30% or greater increase in mean negative mood symptom scores (depression or anxiety), as measured by visual analogue scales, in the week before menses as compared with the week following menses. All PMS patients were medication free and were determined to be free of current or recent (within the past 2 years) medical or psychiatric illness; this determination was made in the same manner as with the panic disorder patients and healthy control subjects. It should be noted that the PMS patients were chosen on the basis of their demonstrating a consistent premenstrual worsening in mood. Therefore, by definition, it would be expected that these subjects would exhibit a premenstrual worsening in visual analogue scale scores. These subjects thus serve as a symptomatic comparison group.

All subjects gave written informed consent to participate in this study.

Procedure

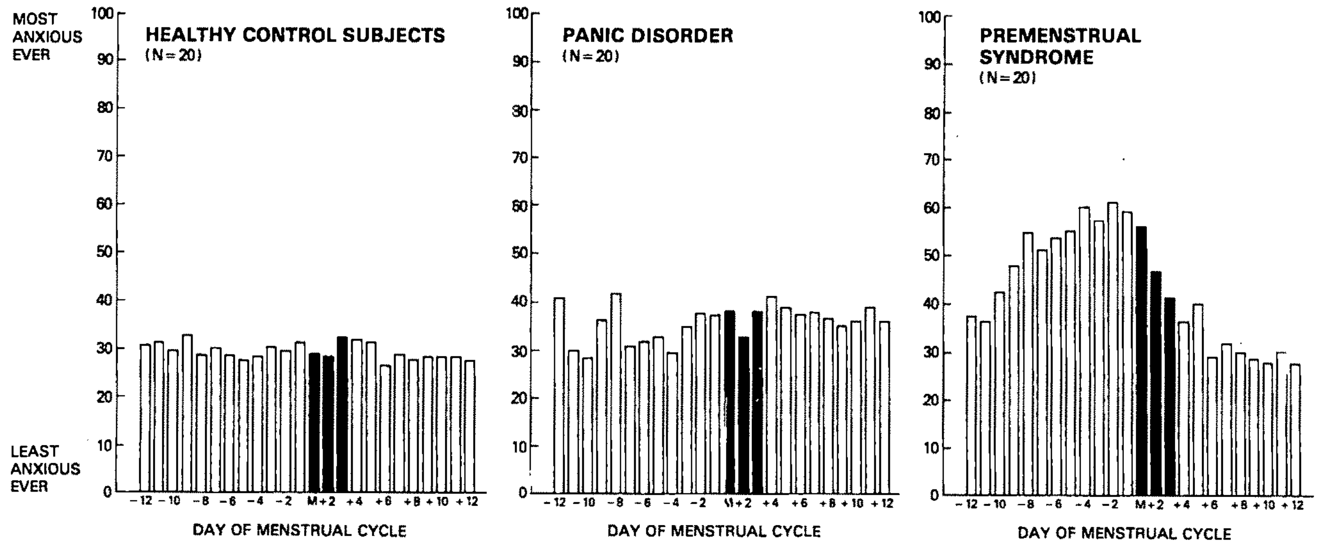
All subjects completed ratings of their generalized anxiety on a daily basis each morning by using visual analogue scales, i.e., 100-mm lines on which subjects are instructed to mark off their current degree of symptoms on a continuum of "least ever" on the left to "most ever" on the right. All subjects recorded the dates of their menses for each menstrual cycle. As previously indicated, ratings took place for two or three menstrual cycles for each subject. Patients with panic disorder completed daily ratings of their anxiety by using the Spielberger State-Trait Anxiety Inventory, State Form, and completed a record of the occurrence of panic attacks (NIMH Panic Attack Scale).

Each day of symptom recording was assigned a position relative to the first day of menstruation. The ratings over several cycles (i.e., two or three) for each day relative to menstruation were averaged, and a mean value was then calculated for each cycle day for each of the three diagnostic groups.

For the panic disorder patients only, mean daily anxiety ratings and the mean number of panic attacks experienced were compared during late luteal (days −7 to −1, i.e., the week before menses) and mid-follicular (days +5 to +11) phases of the menstrual cycle; these phases represented premenstrual and postmenstrual epochs, respectively. Paired t tests (two-tailed) were used to assess differences in the anxiety inventory ratings in the two epochs under consideration. Because the number of panic attacks was not normally distributed, the nonparametric Wilcoxon signed-rank test was used to compare the panic attack frequency in the two epochs under consideration.

In order to compare visual analogue scale anxiety ratings across the menstrual cycle among the three diagnostic groups, the mean mood ratings for the 12 days before menstruation (days −12 to −1) and the 12 days after the onset of menstruation (days +1 to +12) were selected for analysis. We chose a 12-day interval to increase the probability that the days before and after menstruation would correspond to the luteal and follicular phases, respectively, with little overlap. Individual mean anxiety ratings for each menstrual day were then averaged by group to produce group mean daily mood ratings. Group mean anxiety ratings with reference to menstruation were analyzed by two-way analysis of variance (ANOVA) with repeated measures (Group, Time, Group by Time); a correction for repeated measures (24) was used and is reflected in the p values reported. The 24 cycle days under consideration (i.e., days −12 through +12) were also broken into four epochs (days −12 to −7=epoch 1, days −6 to −1=epoch 2, days +1 to +6=epoch 3, and days +7 to +12=epoch 4); epoch 2 is representative of the late luteal or premenstrual phase, and epoch 4 is representative of a late follicular phase. These group mean anxiety ratings were then analyzed by two-way ANOVA with repeated measures (Group, Epoch, Group by Epoch); a correction for repeated measures (24) was used. The latter analysis allowed us to then determine, by post hoc t test (Bonferroni t test), differences between epochs, without the problem inherent in the multiple comparisons needed to examine the 24-day ANOVA described earlier. We also calculated the percentage change from epoch 2 to epoch 4 for each subject; this represents a measure of premenstrual worsening of anxiety relative to the individual's mean symptoms across the entire menstrual cycle. For the latter analysis, percentage change was calculated by using only the range of the visual analogue scale that each individual subject used throughout the study.

FIGURE 1. Mean Daily Anxiety Ratings Across the Menstrual Cycle[a] in Healthy Control Subjects, Patients With Panic Disorder, and Patients With Premenstrual Syndrome



[a]Black bars and "M" indicate menses.

This was done to decrease interindividual variability (18).

All values are reported as mean±SD. All tests are two-tailed, and all p values above 0.10 are reported as nonsignificant.

RESULTS

Panic Disorder Patients

At the time of initial presentation, six panic disorder patients retrospectively reported that their anxiety symptoms were moderately or much worse during the premenstrual phase, while nine felt that their anxiety was only minimally or not at all worse during the premenstrual phase; this information was not available for five patients. The panic disorder patients were evaluated for a mean of 2.45±0.5 (range=two to three) drug-free menstrual cycles. They did not experience a significant change in anxiety ratings between the late luteal and follicular phases of the menstrual cycle (47.4±10.7 versus 48.4±11.6; t=0.46, df=18, $p>0.10$; paired t test). They also did not experience a significant change in the frequency of panic attacks between the late luteal and follicular phases of the menstrual cycle (0.85±1.34 versus 0.79±1.34, $p>0.10$; Wilcoxon ranked-pair test).

Comparison Between Diagnostic Groups

The mean ages of the three groups did not significantly differ (F=0.90, df=2, 57, $p>0.10$). The mean daily anxiety ratings for each of the three groups during days −12 (before menstruation) through +12 (after menstruation) are shown in figure 1. The ANOVA revealed a trend toward a main effect of diagnosis (F=3.10, df=2, 50, $p<0.06$), a significant main effect of time (F=5.03, df=23, 1150, $p<0.0001$), and a significant Diagnosis by Time interactive effect (F=6.08, df=46, 1150, $p<0.0001$).

In order to allow for a more manageable comparison of precisely where the differences revealed by the preceding ANOVA lay, we also used an ANOVA to look at the same data broken into four epochs, as previously described. This allowed us to discern significant differences without having to encounter a large number of multiple comparisons. This ANOVA revealed a trend toward a main effect of diagnosis (F=2.64, df=2, 57, $p<0.09$), a significant main effect of epoch (F=10.18, df=3, 171, $p<0.0001$), and, most importantly, a significant interactive effect of Diagnosis by Epoch (F=13.22, df=6, 171, $p<0.0001$). As shown in figure 2, this analysis indicates that normal control subjects and patients with panic disorder did not show statistically significant fluctuations in anxiety over the menstrual cycle, whereas PMS patients had a robust, statistically significant (i.e., Bonferroni t test requiring $p<0.008$) premenstrual exacerbation of anxiety (epoch 1 versus epoch 2, paired t=3.59, $p<0.002$; epoch 2 versus epoch 3, paired t=4.71, $p<0.0002$; epoch 2 versus epoch 4, paired t=6.17, $p<0.0001$ [df=19 for all paired t tests]).

In addition, the premenstrual percentage change in anxiety was calculated for each subject relative to her range of anxiety observed throughout the entire cycle. These results are illustrated in figure 3 for each of the three diagnostic groups; positive values indicate a premenstrual worsening. Normal control subjects and panic disorder patients had relatively small premenstrual changes (controls subjects: 3.2%±9.2%; panic disorder patients: −3.2%±12.7%), with some pa-

FIGURE 2. Anxiety Ratings During Four Phases of the Menstrual Cycle in Normal Control Subjects, Patients With Panic Disorder, and Patients With Premenstrual Syndrome

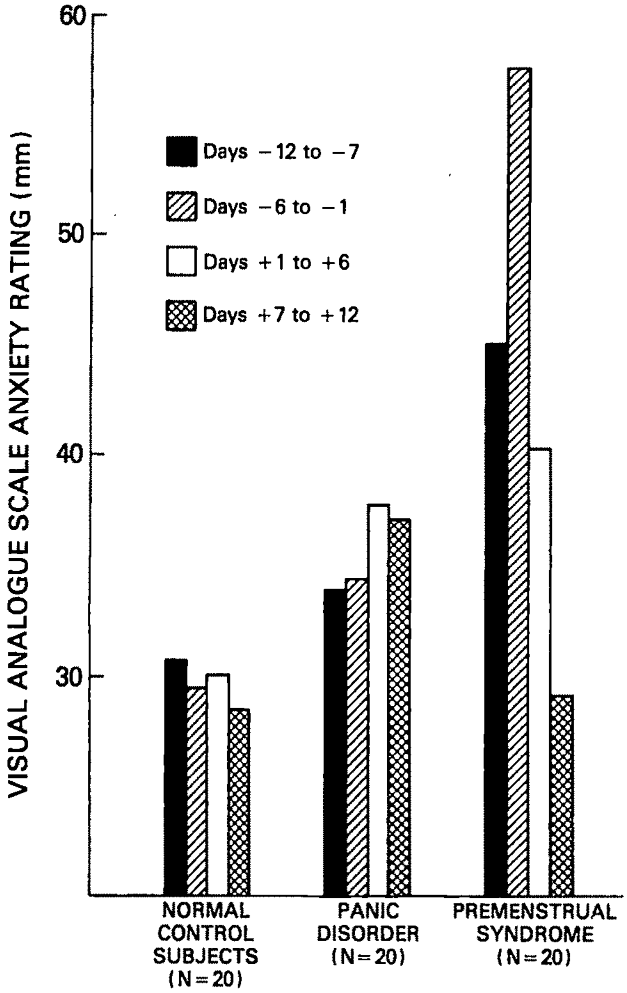
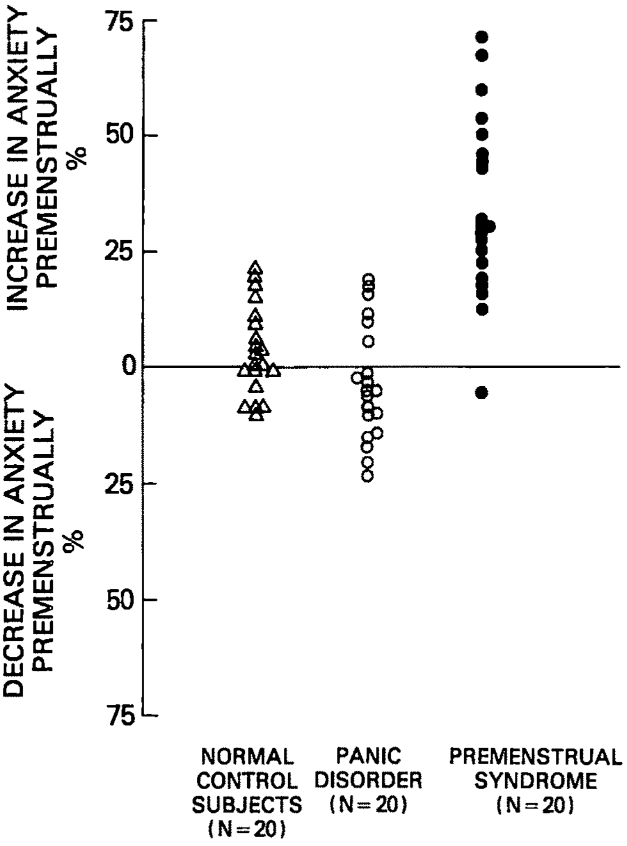


FIGURE 3. Premenstrual Changes in Anxiety, Relative to Each Subject's Range of Anxiety During the Entire Menstrual Cycle, in Normal Control Subjects, Patients With Panic Disorder, and Patients With Premenstrual Syndrome



tients getting marginally better and some marginally worse. In contrast, the PMS patients showed much larger and more consistent premenstrual worsening (34.9%±20.1%; H=33.71, df=2, p<0.0001, Kruskal-Wallis ANOVA); 19 of 20 (95%) of the PMS patients exhibited a premenstrual exacerbation of anxiety (figure 3).

Finally, we examined the relationship between panic disorder patients' retrospective beliefs and the prospective findings. Using even a liberal definition of prospectively determined worsening in anxiety ratings (10%), we found no significant relationship between the retrospective and prospective determinations of premenstrual worsening (p>0.10; Fisher's exact test, one-tailed).

DISCUSSION

In this study of 20 drug-free subjects with panic disorder, we found little evidence to support an influence of the menstrual cycle on symptoms. From several perspectives, including ratings of anxiety and actual panic attack frequency, the anecdotally reported premenstrual exacerbation was not observed. In contrast, a group of 20 drug-free subjects with PMS were shown to have a robust premenstrual increase in anxiety, suggesting that our behavioral measurements were sensitive enough to detect changes in this area. Consequently, we must conclude that, at least for most patients with panic disorder, panic anxiety does not worsen premenstrually. Of course, we cannot discount the possibility that some patients may genuinely exhibit a premenstrual worsening of panic anxiety. Our results suggest, however, that such patients would be the exception, rather than the rule. Yet, as we and others have indicated (14, 19), panic disorder patients frequently believe that they are more symptomatic premenstrually. How can we account for this apparent discrepancy?

Investigations of women complaining of PMS have demonstrated that many of these individuals fail to show any specific relationship between menses and their mood symptoms when studied prospectively. When prospective diagnostic criteria were applied, 50%–76% of subjects who had a history of PMS failed to show evidence of this during longitudinal, prospective ratings (15–18, 23). Thus, there is a precedent for subjects to mistakenly attribute symptom fluctuations to timing of the menstrual cycle. While the reasons for this are not clear, it has been hypothesized that individuals may tend to falsely remember a randomly occurring event as being paired with another salient event if at some point they occur in temporal contiguity (25). The menstrual cycle, by virtue of its being a regularly occurring, noticeable event, may serve as an "anchoring point" for panic disorder patients to try to explain the occurrence of their symptoms. An even more speculative hypothesis is that the current notoriety that PMS has gained in the popular literature may foster this sort of misattribution.

In any case, our findings for panic disorder are quite consistent with the findings in the PMS literature; i.e., most individuals who complain of menstrually related psychiatric symptoms fail to show this pattern when studied prospectively. Our observations underscore the need for prospective assessment of patients with panic disorder (and, indeed, any psychiatric complaints) before concluding that a premenstrual worsening is operative.

Even though panic disorder does not seem to worsen premenstrually, this should not suggest that female reproductive endocrine events play no role in the course of panic disorder. To the contrary, the severity and course of panic disorder have been reported to be affected by pregnancy (26) and the postpartum period (27). Estrogen replacement therapy has also been implicated in the development of some cases of panic disorder (28). Furthermore, we have observed that some women develop panic attacks perimenopausally; in addition, the phenomenologic overlap between some climacteric symptoms (e.g., hot flashes) and panic attacks is quite striking. While preliminary, these observations suggest that the book on panic disorder and reproductive endocrine physiology should not yet be closed. Our efforts to further define this relationship may lead to a better understanding of the pathophysiology of panic disorder, an illness that shows considerable gender specificity.

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Family History of Anxiety Disorders in Control Subjects With Lactate-Induced Panic Attacks

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The authors infused 45 control subjects with sodium lactate. Eight of 10 subjects with lactate-induced panic attacks and 26 of 35 without panic attacks were interviewed. An investigator, blind to the outcome of the infusion study, obtained family histories of 160 relatives. There was a high prevalence of anxiety disorders among first-degree relatives of subjects with panic attacks. There was no significant difference in the prevalence of mood disorders and substance abuse between first-degree relatives of subjects with (N=45) and without (N=115) panic attacks. The results suggest that individuals with a family history of anxiety disorders may be vulnerable to lactate-induced panic attacks.

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Anxiety disorders are quite common. Robins et al. (1) estimated that the lifetime prevalence of anxiety disorders varies from 10% to 25%, with a lifetime prevalence of panic disorder of about 1.5%. Many people may also experience anxiety symptoms or sporadic panic attacks without meeting the diagnostic criteria for panic disorder. In one study (2), 34.4% of presumably normal young adults had experienced one or more panic attacks within the preceding year.

We infused 45 healthy control subjects with sodium lactate, isoproterenol, and dextrose. Ten of the control subjects (22.2%) experienced panic attacks during the sodium lactate infusion (3, 4). Because of the occurrence of sporadic panic attacks in the "normal population," it is possible that the lactate-induced panic attacks in control subjects may reflect a population of people with a vulnerability for panic disorder. Lactate-induced panic attacks may also be suggestive of a continuous spectrum of anxiety from single symptoms or sporadic attacks to a fully developed disorder.

It would be useful and interesting to determine whether this vulnerability is associated with a large genetic load. Six studies have suggested a high rate of familial heredity of anxiety disorders (5–11). These studies primarily reported a high rate of anxiety disorders in first-degree relatives; one study (6) found a high rate of anxiety disorders in second-degree relatives. Torgersen (10) reported that monozygotic twins had a higher frequency of anxiety disorders than dizygotic twins. He also reported (11) that panic disorder patients had a higher familial rate of affective disorders and alcoholism than patients with generalized anxiety disorders. Norton et al. (12) found that subjects with infrequent panic attacks had a significantly higher proportion of first-degree relatives who experienced panic attacks than did subjects without panic attacks.

To our knowledge, no one has examined the family history of control subjects with lactate-induced panic attacks. We compared the prevalence of a family history of anxiety and other mental disorders in control subjects with and without lactate-induced panic attacks.

METHOD

This investigation was part of a double-blind, randomized study of sodium lactate, isoproterenol, and dextrose (placebo) infusions in panic disorder patients and healthy control subjects. The study was approved by the Lafayette Clinic Institutional Review Board, and all subjects gave written informed consent before their participation in the study. On entering the infusion study, control subjects were physically healthy, did not take any psychotropic medication for at least 2 weeks before the infusion, and reported no personal history of panic disorder or other mental illness. The infusion procedure has been described in detail elsewhere (3, 4). Ten of 45 nonpsychiatric control subjects in our study experienced panic attacks during lactate infusion. The family history part of the study was done only after completion of the infusion part of the study, a time interval of several years for some subjects.

We were able to contact nine control subjects with lactate-induced panic attacks. One woman refused to

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be interviewed, and another woman refused to continue in the middle of the interview. We were unable to contact one woman with lactate-induced panic attacks. Thus, we were able to obtain family histories of eight subjects with panic attacks (seven complete, one incomplete). The subjects were five men and three women, with a mean±SD age of 35.1±6.2 years. We obtained histories of 45 first-degree relatives (25 men and 20 women). Forty-three relatives were alive; their mean±SD age was 46.2±20.6 years.

We were able to contact 28 control subjects without lactate-induced panic attacks. One man and one woman refused to be interviewed. One woman was adopted and did not know her biological family. We were unable to contact four men and three women without panic attacks. Thus, we were able to obtain complete data for 25 subjects without panic attacks. The subjects were 17 men and eight women, with a mean±SD age of 34.6±7.9 years. We obtained histories of 115 first-degree relatives (59 men and 56 women). One hundred nine were alive; their mean age was 40.3±19.9 years.

All subjects were contacted by telephone, since some of them were no longer in the area. It is possible to reliably make a lifetime diagnosis of anxiety disorder, major depression, and substance abuse in a family study by using the telephone interview (13).

All probands were interviewed for about 30–60 minutes by the same person. The interviewer was blind to the outcome of the infusion study and did not know the subjects from other experiments. The interviewer explained the nature of the study and asked the interviewed subject not to say anything about the outcome of the infusion study in order to ensure the interviewer's blindness. Initially, an experienced clinician assisted in the whole interview on another telephone line to ensure interview reliability.

The informed consent to participate in this part of the study was obtained over the telephone at the beginning of the interview. All subjects were given a semistructured interview based on the Family Informant Schedule and Criteria (14) (permission to use this tool from Dr. J. Endicott). The interview focused on first-degree relatives. Each subject was interviewed in the same fashion about his or her father, mother, brothers, sisters, and children. Individual results were scored on the Family Informant Schedule and Criteria summary data sheet.

After all the data were collected, the definite, probable, and possible diagnoses were determined for each subject's first-degree relatives. This was done in a blind, independent fashion by two experienced clinicians using the criteria from the Family Informant Schedule and Criteria.

Two-tailed t tests were used to compare the ages in both control groups and in both relative groups. Two-tailed Fisher's exact tests and two-tailed chi-square analyses were used to compare sex distribution in control and relative groups. One-tailed Fisher's exact tests were used to compare frequencies of anxiety disorders, affective disorders, and substance abuse diagnoses in relatives of subjects with and without panic attacks.

RESULTS

There was no statistically significant difference between the ages of control subjects with and without panic attacks ($t=0.18$, $df=31$) and between the ages of relatives of both groups of control subjects ($t=1.63$, $df=151$). There was also no statistically significant difference in sex distribution between the two groups of control subjects (Fisher's exact test, two-tailed) and between relatives of both groups of control subjects ($\chi^2=0.23$, $df=1$, two-tailed).

There was no significant difference in prevalence of all affective disorders between relatives of subjects with (N=8) and without (N=17) panic attacks (Fisher's exact test, one-tailed). There was also no significant difference in prevalence of all diagnoses of substance abuse between relatives of subjects with (N=6) and without (N=9) panic attacks (Fisher's exact test, one-tailed).

There was no significant difference in family history of anxiety disorders between subjects with panic attacks (N=5) and those without panic attacks (N=7) (Fisher's exact test, one-tailed). However, there was a statistically significant difference in prevalence of all anxiety disorders between the two groups of relatives ($p<0.007$, Fisher's exact test, one-tailed); the relatives of subjects with panic attacks were more likely to have an anxiety disorder diagnosis. The difference remained significant even after removal of subjects with the diagnosis of separation anxiety disorder ($p<0.03$, Fisher's exact test, one-tailed). Anxiety disorders were found in 24.4% (N=11) of the relatives of subjects with panic attacks (20% [N=9] without separation anxiety) and in 7.8% (N=9) of the relatives of subjects without panic attacks (6.9% [N=8] without separation anxiety) (see table 1).

DISCUSSION

Our study was limited by two factors. First, both control groups were relatively small, and even with the fair number of relatives, the study results may be influenced by type II error. The second factor limiting the results of our study is the fact that we interviewed only probands and not their relatives. This method is likely to underestimate the prevalence of psychiatric morbidity in relatives. The impaired recall of a proband might influence the reported prevalence, but this would be true for both groups.

To our knowledge this is the first study of the prevalence of anxiety disorders in relatives of healthy control subjects who experience lactate-induced panic attacks. We found a higher prevalence of anxiety disorders among first-degree relatives of subjects with

TABLE 1. Anxiety Disorders in First-Degree Relatives of Control Subjects With and Without Lactate-Induced Panic Attacks

Diagnosis	Relatives of Subjects With Panic Attacks (N=45)			Relatives of Subjects Without Panic Attacks (N=115)		
	Definite	Probable	Possible	Definite	Probable	Possible
Panic disorder	1	0	1	2	1	0
Generalized anxiety disorder	1	0	1	0	0	0
Simple phobia	1[a]	2	0	3	0	0
Posttraumatic stress disorder	0	0	2	0	0	2
Separation anxiety disorder	1	1	0	0	1	0

[a] This relative also met the criteria for probable diagnosis of generalized anxiety disorder.

panic attacks than among first-degree relatives of subjects without panic attacks.

Anxiety disorders are more common in women, and studies suggest a male/female ratio for panic disorder and agoraphobia of 1:3 (1, 7, 15). The prevalence of anxiety disorders can also be influenced by the age of subjects. The age at onset of panic disorder averaged about 24 years and was below 40 years in 96% of the patients in a study by Sheehan et al. (16). The onset of phobias was more equally distributed across age groups (16). Differences in sex and age distribution did not have an important role in our population because sex and age distribution were similar in both groups of probands and both groups of relatives. The ages of probands and relatives in our study are similar to the ages of probands and relatives in a study by Noyes et al. (9).

The rates of anxiety in our study are comparable to rates from studies of panic disorder patients. Noyes et al. (5) reported a morbidity risk of 18% for anxiety neurosis among relatives of neurotic patients and 3% among relatives of control subjects (with questionable cases of 26% and 6%, respectively). The morbidity risks among relatives of panic disorder patients and relatives of control subjects were 24.7% and 2.2%, respectively, in a study by Crowe et al. (7) and 33% and 15% in a study by Harris et al. (8). Noyes et al. (9), in their final report with a bigger patient sample, found morbidity risks for anxiety disorders of 17.3% among relatives of panic disorder patients and 4.2% among relatives of control subjects. The lifetime prevalence of anxiety disorders reported by Robins et al. (1) was between 10% and 25% (depending on the site). Our prevalence rate of about 20% in middle-aged relatives is similar to the prevalence of anxiety disorders in the relatives of panic disorder patients.

Control subjects with lactate-induced panic attacks represent an interesting population of subjects who may have a high vulnerability and predisposition to panic disorder. Norton et al. (2) found a high rate of sporadic panic attacks among college students. They also found (12) that these subjects with infrequent panic attacks are much more likely than subjects without panic attacks to have parents who suffer from anxiety or depressive disorder. We found that a family history of anxiety disorders was more common among subjects with than without panic disorder (62.5% versus 28%), but this difference was not significant. This, together with our finding of a high prevalence rate of anxiety disorders in the relatives of control subjects with panic attacks, suggests that there is a wide spectrum in the presentation of symptoms in genetically predisposed individuals. Our findings also suggest that lactate-induced panic attacks in control subjects may be a trait marker for genetic vulnerability to anxiety disorders.

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A Longitudinal Assessment of Haloperidol Doses and Serum Concentrations in Asian and Caucasian Schizophrenic Patients

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Over 3 months, 13 Caucasian and 16 Asian schizophrenic patients were sequentially treated with weight-adjusted fixed doses and clinically determined, variable doses of haloperidol. During the fixed-dose phase, Asians had a slightly higher mean serum haloperidol concentration and a significantly higher rating for extrapyramidal symptoms. During the variable-dose phase, the Asian patients' mean required dose was significantly lower, resulting in lower serum haloperidol concentrations at the first emergence of extrapyramidal symptoms and for optimal clinical response. These results indicate pharmacodynamic differences in therapeutic response but no significant difference in steady-state serum concentration between the two groups.

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Clinical reports over the past several decades (1, 2) indicate differences between Asian and Caucasian psychiatric patients in therapeutic neuroleptic dose. With a few exceptions (3 and unpublished data of Lu et al.), these clinical observations and surveys have suggested that, as compared to Caucasians, Asian patients generally respond to substantially lower doses of neuroleptics (4–11) and manifest more severe extrapyramidal symptoms when treated with comparable doses (12).

Corresponding to these clinical reports, our recent study involving healthy Asian and Caucasian male volunteers (13) revealed significantly higher mean serum haloperidol and prolactin concentrations in Asians after either an oral or intramuscular dose of haloperidol. These differences remained statistically significant after we controlled for body surface area. Further, prolactin response to haloperidol was significantly greater in Asians even after haloperidol concentration was taken into account. These findings clearly demonstrate a significant difference between Asians and Caucasians in their response to haloperidol challenge. They further suggest that both pharmacokinetic and pharmacodynamic factors contribute to such differences in response to haloperidol.

For findings derived from this single-dose study with normal volunteers to be clinically relevant, they obviously have to be validated in clinical situations. To do so, we prospectively studied a group of Asian and Caucasian schizophrenic patients who were treated by means of a predetermined protocol and assessed them longitudinally with standard rating instruments for clinical response and side effects. Blood samples were obtained simultaneously for the determination of serum haloperidol concentrations.

METHOD

All participating subjects signed written informed consent statements before entering the study. Only Asian and Caucasian patients with homogenous parentage and definitive diagnoses of schizophrenia or schizophreniform disorder according to *DSM-III* were included in the study. For the establishment of the diagnosis, each subject was interviewed with the Structured Clinical Interview for *DSM-III* (SCID) (14) before he or she entered the study. Also performed at this time were a physical examination and routine laboratory tests, which included electrolyte measurements, liver and thyroid function tests, complete blood count, urinalysis, and toxicology screening. All participants included in the study were physically healthy and had no history of substance abuse. At the beginning of the study, all subjects manifested active symptoms as defined in the A section of the *DSM-III* criteria, and their initial total scores on the Brief Psychiatric Rating Scale (BPRS) (15) were all higher than 25.

Twenty-nine psychiatric patients fulfilled the criteria for the study. Of these, 13 were Caucasians and 16 were Asians. The Asian subjects included five Chinese, four Japanese, two Filipino, one Korean, and four Vietnamese. The Caucasian and Asian groups were

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TABLE 1. Characteristics of Caucasian and Asian Schizophrenic Patients Given Haloperidol at Fixed[a] and Clinically Determined Doses

	Caucasians (N=13)		Asians (N=16)			
Characteristic	Mean	SD	Mean	SD	t (df=27)	p
Weight (lb)	173.5	42.0	130.1	16.1	3.53	0.0005
Height (inches)	68.3	3.6	64.7	3.5	2.73	0.003
Body surface area (m^2)	1.92	0.25	1.64	0.12	3.71	0.003
Length of illness (months)	89.1	73.9	87.8	117.4	0.04	n.s.
Length of neuroleptic exposure (months)	55.8	62.6	54.9	103.3	0.03	n.s.
Total BPRS score at admission	36.8	8.7	34.7	7.8	0.66	n.s.
Percentage change in total BPRS score						
Fixed-dose phase[a]	28.0	10.2	28.9	17.2	−0.17	n.s.
Neuroleptic threshold[b]	27.5	21.4	35.9	19.1	−1.03	n.s.
Optimal dose[c]	48.7	11.2	49.7	13.5	−0.23	n.s.
Haloperidol dose (mg/day)						
Fixed-dose phase[a]	11.8	2.9	8.9	1.1	3.47	0.005
Neuroleptic threshold[b]	11.5	4.1	6.5	3.4	3.44	0.005
Optimal dose[c]	14.3	8.5	5.1	3.3	3.88	0.001
Haloperidol serum concentration (ng/ml)						
Fixed-dose phase[a]	6.0	2.5	6.8	2.2	−0.90	n.s.
Neuroleptic threshold[b]	7.8	4.6	4.3	3.1	2.46	0.02
Optimal dose[c]	7.6	6.6	3.6	2.9	2.20	0.05
Score on Neurological Rating Scale (two items)						
Fixed-dose phase[a]	0.29	0.38	0.82	0.73	−2.46	0.03
Neuroleptic threshold[b]	0.23	0.44	0.38	0.62	−0.73	n.s.
Optimal dose[c]	0.67	0.89	0.67	0.90	0.00	n.s.

[a] Fixed dose=0.15 mg/kg of body weight per day.

[b] The neuroleptic threshold was the dose at which the patient did not require anticholinergic medication and manifested minimal extrapyramidal symptoms (Neurological Rating Scale wrist and elbow item scores totaling 0 or 1 and total score of 8 or less).

[c] The optimal dose was the dose at the point of the lowest total BPRS score.

similar in age distribution (mean±SD=34.1±8.4 and 33.8±12.6 years, respectively; t=0.07, df=27, n.s.) and ratio of men to women (3:10 and 6:10; χ^2=0.02, df=1, n.s.). As shown in table 1, however, the Caucasians were significantly heavier and taller than the Asians. These differences in body build resulted in a statistically significant difference in body surface area between the Asians and Caucasians, which was used as a covariate in the analysis of ethnic differences in therapeutic haloperidol dose and serum concentrations. The two groups were similar in mean length of illness, duration of previous neuroleptic exposure, and initial level of psychopathology (table 1).

Twelve of the 29 subjects—five Caucasians (38%) and seven Asians (44%)—had been drug-free for at least 3 months before the study (χ^2=0.08, df=1, n.s.). In addition, neuroleptics were withheld from five Asians and four Caucasians for 2 weeks before they entered the study. The remaining eight patients (four Asians and four Caucasians) continued to receive their previous medication. However, subsequent data analysis revealed no apparent differences between patients with and patients without the washout.

The patients were treated with haloperidol and followed for approximately 3 months. The treatment was divided into an initial fixed-dose phase and a subsequent variable-dose phase. The fixed-dose phase immediately followed intake and lasted for 2 weeks, during which time the subjects were treated with oral haloperidol in tablet form. The dose was 0.15 mg/kg of body weight per day. Starting from the third week of the study, the dose of haloperidol was adjusted weekly or biweekly according to the patient's clinical condition. Benztropine, 4.0 mg/day, was given routinely in the first 2 weeks for the prevention of acute dystonia. It was discontinued at the end of the second week unless clinically indicated. Throughout the treatment repeated attempts were made to discontinue the use of benztropine as soon as it seemed tolerable for the subject so that extrapyramidal symptoms could be accurately assessed.

Clinical interviews were conducted weekly or biweekly in the morning approximately 12 hours after the last dose of haloperidol. Each session began with the drawing of a 10-ml blood sample for the measurement of serum haloperidol. After the blood drawing, the subject's clinical status was assessed with the BPRS. Extrapyramidal symptoms were evaluated with the Neurological Rating Scale (16) and the Abnormal Involuntary Movement Scale (AIMS) (17). Other side effects and dose were recorded on a modified version of the Dosage and Treatment Emergent Symptoms Scale (17). The subject was also asked to record the exact amount and timing of medications (haloperidol and benztropine) taken between interviews, and a pill count was performed after each interview.

On the basis of the ratings, we established three time-points for comparison of clinical outcome, side effects, haloperidol dose, and serum haloperidol concentration. These were termed fixed-dose phase, neuroleptic threshold point, and optimal response point. Respectively, these three comparison points provided information regarding whether there were ethnic differences in steady-state haloperidol concentration, extrapyramidal symptoms, or clinical response. Since the subjects were assessed twice during the fixed-dose phase, the means of the two ratings and the two serum haloperidol concentrations were used in the statistical analyses. The neuroleptic threshold was defined according to Haase and Janssen (18) and McEvoy et al. (19) as the highest haloperidol dose at which the patient did not require anticholinergic medication and manifested minimal extrapyramidal symptoms. This point was operationally defined as a total score of 0 or 1 (maximum possible=8) on the two most sensitive items (wrist and elbow) of the Neurological Rating Scale (G.M. Simpson, personal communication, 1987). The optimal response point was defined as the point when the patient had the lowest total BPRS score. The dose at this time was usually also the maintenance dose the subject continued to receive after completing the research protocol. When more than one assessment point fulfilled the criteria, the means of the ratings and concentrations were used for the analyses. Figure 1 depicts the longitudinal course of a representative patient and how these three assessment points relate to haloperidol dose, haloperidol serum concentration, benztropine dose, clinical outcome, and side effect status over the treatment course.

For each subject the relative haloperidol concentration at each treatment session during the variable-dose phase was calculated by dividing the haloperidol concentration by the dose given during the preceding week. The average of these relative concentrations was then calculated for each subject for subsequent analysis.

The blood samples were allowed to clot overnight at 4 °C and were then centrifuged at 500 *g* for 30 minutes, and aliquots of the serum were frozen at −20 °C. Serum haloperidol was measured by means of radioimmunoassay (20). The maximum intra- and interassay coefficients of variations were 9% and 13%, respectively. All samples from each subject were analyzed in the same assay. All clinical and laboratory data were analyzed with the CRISP (21) and BMDP (22) software programs. Analysis of covariance (ANCOVA) (21, 22) and Student's two-tailed t tests were used to compare the two ethnic groups. Data that were not Gaussian distributed were log-transformed before statistical analysis. Significance levels of $p \le 0.05$ were considered statistically significant.

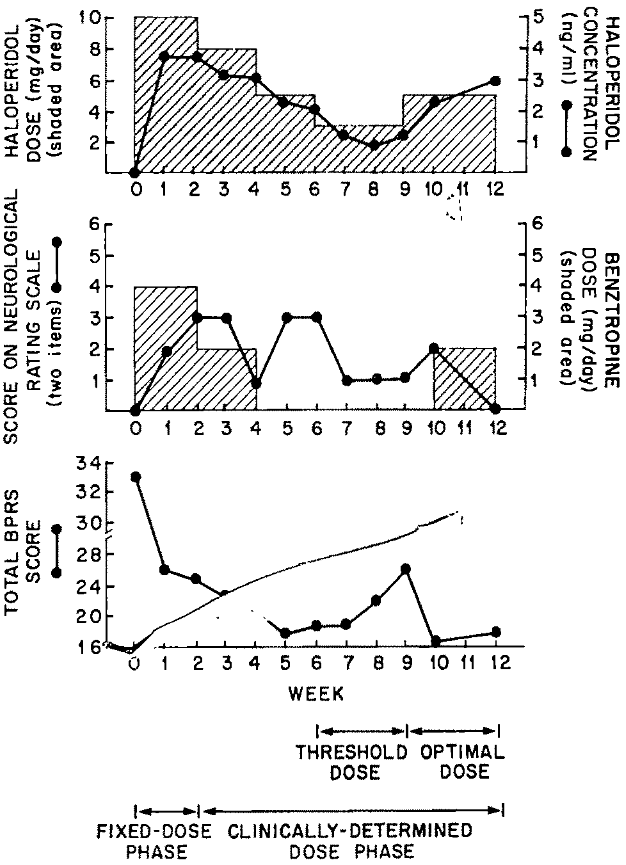
RESULTS

As shown in table 1, the Caucasian and Asian patients' clinical responses, as evidenced by the percentages of reduction in their total BPRS scores, were similar at the neuroleptic threshold and optimal response points during the variable-dose phase of the study.

The mean haloperidol dose for the Asians was significantly lower than that for the Caucasians at each of the three assessment points (fixed-dose, neuroleptic threshold, and optimal response) (table 1). After we entered body surface area as a covariate, these differences remained statistically significant at both the neuroleptic threshold and optimal response points (F=13.48, df=1, 26, $p<0.001$ and F=4.34, df=1, 26, $p<0.05$, respectively) but not during the fixed-dose phase (F=0.45, df=1, 26).

During the fixed-dose phase, the Asian patients had a slightly higher mean haloperidol concentration, but the difference did not reach statistical significance. In contrast, during the variable-dose phase, the Asians had significantly lower neuroleptic threshold and optimal response haloperidol concentrations (table 1). Although the Asians had a higher average relative haloperidol concentration (mean±SD: 0.88±0.54 versus 0.65±0.40 ng/ml; median: 0.82 versus 0.66 ng/ml), this difference also did not reach statistical significance ($t=1.31$, df=27, $p>0.1$; Mann-Whitney test: $Z=1.71$, df=27, $0.05<p<0.1$). However, statistical power analysis (23) indicated that approximately 60 subjects per

FIGURE 1. Longitudinal Course of a Schizophrenic Patient Given Haloperidol at Fixed and Clinically Determined Doses[a]



[a] Fixed dose=0.15 mg/kg of body weight per day. The threshold dose was the highest dose at which the patient did not require anticholinergic medication and manifested minimal extrapyramidal symptoms (Neurological Rating Scale wrist and elbow item scores totaling 0 or 1 and total score of 8 or less). The optimal dose was the dose at the point of the lowest total BPRS score.

group would be required to reach significance at an alpha of 0.05 and a beta of 0.80.

During the fixed-dose phase, while the two groups also received the same dose (4.0 mg/day) of benztropine, the Asians manifested significantly higher ratings for extrapyramidal symptoms (table 1). This difference remained statistically significant after serum haloperidol concentration was entered as a covariate ($F=4.26$, $df=1, 26$, $p<0.05$). In contrast, no significant differences in side effect ratings were observed during the variable-dose phase.

Neither the length of illness nor the total duration of previous neuroleptic exposure predicted haloperidol dose, haloperidol serum concentration, or side effect status. The significance levels for all such comparisons were $p>0.30$. In addition, the differences between the two groups remained significant when each of these variables was used as a covariate in the statistical analyses.

DISCUSSION

To our knowledge, this is the first prospective study that has attempted to systematically examine in a clinical setting differences in neuroleptic dose between Asians and Caucasians with both fixed- and variable-dose regimens. Such a design enabled us to directly compare and contrast factors affecting the steady-state haloperidol concentrations and pharmacodynamic factors that might contribute to differences in clinical response between the two ethnic groups. By manipulating and then accounting for haloperidol dose and serum concentration, clues as to whether differential drug responses are caused by differences in steady-state concentrations or by dynamic factors can be assessed. If only the former is the case, Asians should have significantly higher serum haloperidol concentrations than Caucasians when doses are fixed but similar concentrations when the doses are clinically determined. If the latter is true, there should be no ethnic difference in serum haloperidol concentrations when the doses are fixed, but Asians should have significantly lower optimal and neuroleptic threshold haloperidol concentrations when the doses are clinically determined. Finally, as suggested in our previous study with normal volunteers (13), if the kinetic and dynamic factors work together to produce a lower required haloperidol dose in Asians, Asians should have significantly higher haloperidol concentrations when the doses are fixed but lower concentrations when the doses are clinically determined.

Confirming earlier reports on substantial differences between Caucasians and Asians in the range of therapeutic neuroleptic doses, our results demonstrate that Asian schizophrenic patients require significantly lower doses of haloperidol for the optimal treatment of their condition. At the same time, the threshold dose, defined as the haloperidol dose required for subclinical extrapyramidal symptoms to emerge (here defined as the point at which very mild rigidity first appears), also was significantly lower in Asians than in Caucasians. These dose differences remained significant after we controlled for the influences of body surface area, as we reported previously in a retrospective clinical study (9).

This ethnic difference in required neuroleptic dose was also clearly reflected in the side effect profiles of the two ethnic groups when the doses were based on weight (fixed-dose phase), as evidenced by a significantly higher incidence of extrapyramidal symptoms in Asians than in Caucasians, even though the Asians actually received higher doses of benztropine according to data adjusted for weight or body surface area. In contrast, when the doses were clinically determined (variable-dose phase) and the serum haloperidol concentrations were lower in the Asians, the side effect profiles of the two groups were strikingly similar. Together, these findings corroborate Binder and Levy's earlier report (12) and suggest that their Asian patients had an alarmingly high incidence of extrapyramidal symptoms because the haloperidol doses those patients received were excessive, possibly because of pharmacodynamic factors.

The Asians in our study also manifested substantially lower serum haloperidol levels during the variable-dose phase. These differences, statistically significant for both the optimal and threshold concentrations, further substantiate the thesis that pharmacodynamic differences exist between Asians and Caucasians (13). These results are also in congruence with our previous finding of higher prolactin concentrations among healthy Asian volunteers than among Caucasian volunteers receiving the same dose of haloperidol. Similar observations on differences between Asians and Caucasians in therapeutic serum concentration have been reported with lithium and tricyclic antidepressants (24–28).

On the basis of findings derived from previous studies (11, 13, 29), we had predicted that the steady-state serum haloperidol concentration during the fixed-dose phase and the relative haloperidol concentration during the variable-dose phase would be significantly higher in Asians than in Caucasians. To our surprise, this did not turn out to be the case. There are several possible reasons for this discrepancy. First, the requirement of a fixed-dose phase at the beginning of treatment might have excluded patients whose metabolism and excretion of haloperidol were substantially different from those of the patients entered into the study. Throughout the study, we repeatedly encountered Asian patients who refused to enter the study because of past experiences of severe extrapyramidal symptoms with "regular" doses of haloperidol. In contrast, several Caucasian patients were not included in the study because they had previously required neuroleptic doses far above those used in the fixed-dose phase of the study. It is possible that the ethnic contrast in the steady-state haloperidol concentrations would have been more dramatic had these patients been included in the study. Second, although single-dose pharmacokinetics have been demonstrated to predict the steady-state serum or plasma concentrations of several psychotropic drugs, including haloperidol (30–32), the exact relationship between acute and chronic dosing remains unclarified, and ethnic differences in the former may not necessarily predict the latter. Third, the patient sample in this study may have been more heterogeneous than the samples in the previous studies and hence may not have been large enough for the testing of ethnic differences in steady-state haloperidol concentrations. Previous clinical studies (11, 29) that have demonstrated such differences have been conducted in Chinese communities outside of the United States. Our study included subjects with other Asian cultural backgrounds as well. This may have been responsible for greater variance, resulting in our failure to demonstrate a statistically significant difference in steady-state haloperidol concentrations.

In summary, the results of this study appeared to confirm previous clinical observations of a significant difference in the range of therapeutic neuroleptic doses between Asians and Caucasians. This difference appears to be determined mostly by ethnic differences in pharmacodynamics. Because of this difference, Asian schizophrenic patients may require lower doses of haloperidol and lower haloperidol concentrations than their Caucasian counterparts for comparable clinical response and side effect profile.

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Diagnostic Legitimacy of Factitious Disorder With Psychological Symptoms

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The authors question the clinical status of factitious disorder with psychological symptoms as a mental disorder. In particular, they argue that unresolved issues regarding the motivational basis of this disorder and the lack of clearly delineated inclusion, exclusion, and outcome criteria seriously compromise its diagnostic legitimacy. Two case reports are presented to illustrate these difficulties. Future studies should consider these empirical and conceptual difficulties in refining the diagnosis of factitious disorder with psychological symptoms for DSM-IV.

(Am J Psychiatry 1989; 146:1312–1314)

The nature of the psychiatric diagnosis has shifted from a clinically intuitive continuum model (*DSM-II*) to a more empirically based, descriptive approach (*DSM-III, DSM-III-R*) with formal inclusion and exclusion criteria. Despite this largely successful attempt to improve diagnostic reliability, several anomalies in the current nosology hark back to unsubstantiated, and perhaps unverifiable, clinical impressions. In our opinion, one such diagnostic throwback is the recent emergence of factitious disorder with psychological symptoms. According to *DSM-III-R*, this disorder is characterized by 1) intentional production or feigning of psychological (but not physical) symptoms, 2) a psychological need to assume the sick role as evidenced by the absence of external incentives for the behavior, such as economic gain, better care, or physical well-being, and 3) occurrence not exclusively during the course of another axis I disorder, such as schizophrenia. It differs from malingering on the basis of an "intrapsychic need" and the absence of external incentives.

The diagnosis of factitious disorder with psychological symptoms appears to be based on the tenuous logic that if you want to be a patient badly enough, then you are mentally ill. Other deliberate attempts to fabricate mental illness are not elevated to the full stature of a mental disorder but receive the often pejorative label of "malingering." Including factitious disorder as a diagnostic category is based on the assumption that playing the mentally ill patient is tantamount to being the mentally ill patient. However, the concept of factitious disorder, for the most part, remains empirically unsubstantiated.

An essential element of a mental disorder is the existence of psychiatric/psychological disturbance, although modifiable for short periods of time (1), beyond the patient's choice. The diagnosis of factitious disorder appears to not meet this precondition. It has been suggested (2) that individuals with factitious disorder consciously fabricate symptoms but are unaware of their motivation to do so. Jonas and Pope (3) made the even stronger argument that patients with factitious disorder, while voluntarily producing symptoms, have an involuntary compulsion to do so that is based on unconscious motivation. This creative attempt to "have it both ways" (voluntary and involuntary) is controversial (4) and appears diagnostically indefensible. Indeed, this point was not lost on Jonas and Pope (3) and Cunnien (5), who concluded that questions of voluntariness and consciousness are likely to evade any objective assessment.

Motivation (conscious or unconscious, voluntary or involuntary) is the determining factor in the diagnosis of factitious disorder with psychological symptoms. We believe that three unresolved issues regarding the motivational basis of factitious disorder must be explicated more clearly before the validity of this disorder can be firmly established. First, because of an individual's deception of others and possible self-deception, the specific motivations for a "factitious presentation," while probably multidetermined, may not be knowable. Second, given our assumptions of multicausality, the thesis that intrapsychic phenomena alone would account for a complex set of interpersonal behaviors is an insufficient explanation. Third, the diagnosis of factitious disorder with psychological symptoms appears to be based on the implicit assumption that such motivation for dissimulation, whether intrapsychic or not, is necessarily maladaptive. An alternative view is that such dissimulation could also be an adaptive approach to overwhelming intrapersonal or interpersonal problems.

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The establishment of factitious disorder with psychological symptoms as a mental disorder also appears to violate the basic principles of diagnosis. As set forth by Syndenham (cited by Murphy et al. [6]), the diagnostic requirements for a disorder are reliable 1) inclusion criteria (i.e., definition of the disorder), 2) exclusion criteria (i.e., differential diagnosis), and 3) outcome criteria (i.e., course of the disorder). In addition, modern investigators look for confirmatory evidence in familial and laboratory studies (7). Factitious disorder with psychological symptoms, with its many variations, does not appear to satisfy the requirements for a mental disorder of inclusion, exclusion, and outcome criteria. For example, an examination of the literature on factitious psychosis or pseudopsychosis (8–10) reveals that these patients appear to have family histories of mental illness and to have concurrent diagnoses. These results suggest the existence of a subgroup of patients for whom simulation of bizarre psychotic symptoms may constitute part of the prodromal phase of a borderline or psychotic disorder.

What is eminently clear is that factitious disorder with psychological symptoms, at least in the case of factitious psychosis, fails to satisfy the formal requirements for a mental disorder on at least two counts. First, the absence of explicit and theoretically defensible inclusion and exclusion criteria militates against a reliable diagnosis. Second, the outcome criteria are counterintuitive in that the existing outcome data are indicative of an ominous deterioration to an underlying borderline or psychotic disorder, rather than a voluntary production of bizarre symptoms. Certainly, the intense instability and frequent manipulativeness of borderline patients calls into question the soundness of diagnosing factitious disorder in the presence of such a disorder.

Likewise, the diagnosis of factitious disorder with psychological symptoms in patients with Ganser syndrome is fraught with difficulties. There continues to be considerable debate over the etiology of Ganser syndrome; suggested underlying disorders range from adjustment disorder to hysterical and dissociative disorders (11–13). Furthermore, the voluntary aspect of its clinical presentation, the pivotal aspect of factitious disorder, remains unresolved and controversial. Even advocates of factitious disorder with psychological symptoms would be hard pressed to argue that the Ganser syndrome satisfies Syndenham's criteria for a diagnosis.

The two case studies we present here exemplify the complexity of diagnosing dissimulation in psychiatric patients. These cases are followed by further discussion of factitious disorder with psychological symptoms and recommendations for further study.

CASE REPORTS

Case 1. Mr. A, a 35-year-old single man, was referred to a large metropolitan forensic service for a 30-day evaluation. Approximately 2 months before this admission he had thrown rocks through a store window in an apparent effort to be institutionalized. He was released from jail after several days and "attempted" to rob a bank (pretending to have a gun). He was subsequently found to be mentally ill and was admitted on a voluntary basis to a psychiatric hospital. Without any observable provocation, he used a dinner knife to assault a fellow patient with whom he was unacquainted. He said he had done this so he would be admitted to a maximum-security forensic hospital because "it's quiet and peaceful." Mr. A had a history of psychiatric treatment spanning 15 years and 14 hospitalizations and had received diagnoses of paranoid schizophrenia, schizoaffective disorder, bipolar affective disorder, antisocial personality disorder, and polysubstance dependence. He also had a long history of contacts with the criminal justice system.

At discharge, Mr. A was diagnosed as having schizoaffective disorder and continued to give markedly unreliable reports. He claimed to have such extraordinary and diagnostically atypical symptoms as hearing the transmission of his thoughts (a whizzing sound) and experiencing the room contracting and expanding in rhythm with his breathing. He appeared ambivalent in his desire for hospitalization and treatment. In a less guarded moment he confided, "When I am inside I want to be outside, and when I am outside I want to be inside."

Mr. A declined psychological testing. Corroboration of his dissimulation was provided by research data based on the Structured Interview of Reported Symptoms (R. Rogers, 1986) and the M Test (14), in which Mr. A claimed inconsistent and highly implausible symptoms.

Case 2. Ms. B, a 32-year-old married woman, was referred for an inpatient forensic evaluation. At issue was her legal sanity, since she was charged with various counts of arson and had allegedly set fire to her home while the rest of her family was sleeping.

Ms. B had been denied admission to a psychiatric facility on the day of the incident. Her various explanations for her fire setting included command hallucinations, sleep walking, undue influence from a horror film, an attempt to ward off her husband's constant sexual demands, and a desperate attempt to obtain hospitalization and necessary treatment.

Her clinical presentation fluctuated dramatically, from quiet withdrawal to intense lability. Although she had been previously diagnosed as having bipolar disorder, her instability of mood, impulsiveness, poor anger control, and past suicidal behavior suggested a borderline personality disorder. Her description of symptoms also varied from day to day. On occasion, she reported bizarre symptoms, such as believing that the furniture was growing, a star was following her wherever she went, and her house was trying to "gobble her up." She did not appear to have any interest in her pending court case but seemed to like the attention she received from the clinical staff. At times she expressed relief from being rescued from her husband's insatiable sexual demands.

Corroborative data from psychological testing (MMPI) and research protocols (M Test and Structured Interview of Reported Symptoms) substantiated her unreliability and likely dissimulation. Her motivation for fire setting and her subsequent clinical presentation during hospitalization may have reflected 1) psychotic turmoil and confusion, 2) general dependency needs, 3) specific attention-seeking behavior, 4) an acute need for treatment and structure, or 5) a sophisticated attempt to escape legal responsibility by "playing crazy."

DISCUSSION

Case 1 exemplifies the highly ambivalent patient whose sole motivation appears to be the adoption of a patient role. What underlies this motivation? The range of options might include 1) inability to cope with the demands of community living, 2) institutional dependency, 3) a desire, however ambivalent, for treatment and improvement, 4) hostility toward staff and/or society, and 5) an impulsive, almost thoughtless, effort to escape from unpleasant circumstances. Which of these would satisfy the inclusion criteria of factitious disorder with psychological symptoms? How could the apparent paradox of Mr. A's unreliable reports and desire for discharge from the hospital be accommodated in the dichotomy of factitious disorder and malingering?

Case 2 underscores the inherent difficulty of establishing motivation for dissimulation in an obviously contradictory patient. At times, Ms. B appeared to be aware of her fantastic symptoms and contradictions. Indeed, she was very willing to recant and provide equally implausible symptoms in an apparent attempt to please the assessment team. What underlay her attempts to be an "agreeable" patient? Explanations might include 1) fear that treatment might be withheld if she offended staff, 2) deterioration in her cognitive functioning, 3) attempts to disengage herself from a court-ordered evaluation, and 4) a sophisticated attempt to appear more mentally ill and thus escape responsibility for her actions.

Both cases highlight the seemingly intractable difficulties in unraveling the motivational drives of deceptive individuals on the basis of the artificial dichotomization (to be or not to be a patient). Mr. A and Ms. B are unlikely to know their motivations or, if they do, are unlikely to express them honestly. Furthermore, such an effort to elucidate motivation obscures the real clinical issues: Are the reported symptoms bona fide? and Will the patient accept and benefit from available treatment?

The validity of factitious disorder with psychological symptoms as a psychiatric diagnosis is questionable on several grounds. First, *DSM-III* achieved unacceptably low kappa coefficients (0.66 and −0.005) on a total of seven patients with factitious disorder (*DSM-III*, p. 470). Second, as clearly observed in Cunnien's scholarly review of factitious disorder with psychological symptoms (5), attempts to generalize from Ganser syndrome and even Munchausen syndrome to the dynamics of factitious disorder with psychological symptoms are unjustified.

Individuals who present with factitious disorder are difficult to manage clinically and to treat. Questions remain as to whether factitious disorder with psychological symptoms is more of a symptom/syndrome than a disorder, since its presentation may be closely allied, if not etiologically linked, with certain borderline (8) and atypical psychotic disorders (7, 10). The relationship of the diagnosis of factitious disorder with psychological symptoms to the factitious presentation of physical symptoms continues to be unresolved (5, 15). Only through standardized approaches (e.g., specially constructed rating scales) to cases presenting as factitious disorder with psychological symptoms would it be possible to assess thoroughly reliability and validity. The validity of the diagnosis of factitious disorder with psychological symptoms will likely need further consideration before it is included in *DSM-IV*.

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A Crosswalk From *DSM-III-R* to *ICD-9-CM*

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The authors describe a crosswalk, or translation, from DSM-III-R *to* ICD-9-CM. *They present differences in the purposes and formatting of these two documents and discuss different levels of compatibility between the two. They demonstrate several problems at the code, rubric, and case levels of compatibility. Ninety-seven percent of* DSM-III-R *codes are compatible with* ICD-9-CM *at the case level. The problems in most cases are minor, and in the authors' opinion are not problems in actual clinical or medical records use. The development of* DSM-IV *and* ICD-10 *should include attention to translation issues early in the process from the perspectives of clinical work, research, and medical records.*

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The development of *DSM-III* has been widely regarded as one of the most important advances in psychiatric nosology (1, 2). Although *DSM-III* has not been without its detractors (3, 4), in general its phenomenologic approach to mental disorder, its use of diagnostic criteria, and its multiaxial evaluation process are generally felt to have greatly advanced the state of the art of "naming" in psychiatry.

DSM-III is the most recent edition of APA's nosological manual. The first edition of APA's *Diagnostic and Statistical Manual* (*DSM-I*) was published in 1952, in a context in which there were four psychiatric classification systems. *DSM-I* pulled together the systems of the American Medical Association, the Armed Forces, and the Veterans Administration. The fourth system was the sixth revision of the *International Classification of Diseases* (*ICD*), the World Health Organization's (WHO) international statistical classification, which is used worldwide. *ICD-6* was essentially left behind by *DSM-I*, since *ICD-6* was not deemed suitable for the degree of advance that had taken place in psychiatric nosology and since mental disorders were scattered throughout the volume.

When the seventh revision of *ICD* contained no revision of the mental disorders portion, the United States and United Kingdom submitted a proposal to WHO for a mental disorders chapter. Much of this proposal eventually became part of the eighth revision of *ICD* (*ICD-8*), which was also published by APA as the almost identical *DSM-II*.

DSM-III was developed in close coordination with the mental disorders chapter of the ninth revision of *ICD (ICD-9)* and especially with the U.S. version, *ICD-9-CM* (the Clinical Modification). *ICD-9-CM* and *DSM-III* are very similar to one another and contain increased specificity over *ICD-9* (which is used in most of the world).

In spite of this coordination in development, however, to many users of *ICD* there were still incompatibilities between *DSM-III* and *ICD-9-CM*. These incompatibilities are important because most reimbursement systems, including Medicare and Medicaid, as well as epidemiologic research programs assessing morbidity and mortality, require the reporting of patient diagnoses by *ICD-9-CM* codes. In response, several federal agencies (the National Institute of Mental Health [NIMH], the National Center for Health Statistics, and the Health Care Financing Administration) developed a translation, or "crosswalk," from *DSM-III* to *ICD-9-CM* (5). This crosswalk demonstrated that although there are discrepancies between *DSM-III* and *ICD-9-CM*, the differences are more apparent than real, with the major problem being new terminology in *DSM-III*, which in most cases corresponds directly with *ICD-9-CM* terms (6).

In 1983 APA began work on a revision of *DSM-III*, which was approved for use in 1986 as *DSM-III-R* (*DSM-III-R*, pp. xix, xxii). In the revision, renewed attempts were made to achieve compatibility with *ICD-9-CM*. For example, unlike *DSM-III*, all *DSM-III-R* codes are legitimate *ICD-9-CM* codes (*DSM-III-R*, p. xxv). However, the revision retains much of the *DSM-III* terminology that differed from *ICD-9-CM*. In addition, new terminology was added and some codes were eliminated from *DSM-III-R*. These and other compatibility problems with *ICD-9-CM* led to calls for a crosswalk from *DSM-III-R* to *ICD-9-CM*. Such a crosswalk was developed and is available from

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the American Medical Records Association. (The *DSM-III-R*to *ICD-9-CM* crosswalk is available from Ms. Rita Finnegan, American Medical Records Association, 875 North Michigan Ave., Suite 1850, Chicago, Ill. 60611.) It will be used in medical records rooms throughout the United States to translate the *DSM-III-R* diagnoses of psychiatrists and other physicians into *ICD-9-CM* codes. The need for this translation has recently increased because of proposed changes in Medicare. These changes would mandate that the exact *ICD-9-CM* code must be used on every physician request for payment submitted under Part B of Medicare (7). Our purpose in this paper is to discuss some of the specific problems dealt with in the crosswalk and evaluate the overall compatibility between *DSM-III-R* and *ICD-9-CM*.

PURPOSE OF *DSM-III-R*

As noted in previous work (6), in evaluating the differences between *DSM* and *ICD*, it is important to distinguish between the purposes of these two documents. *DSM* is a medical nomenclature, or nosology, i.e., a diagnostic manual to be used primarily by clinicians and by clinical and epidemiologic researchers. It presents a limited number of diagnostic categories, with each category representing a syndrome seen by clinicians. In addition, *DSM* attempts to stay abreast of current research in the field of psychiatry, frequently applying new data relevant to assessing and understanding psychopathology. It changes relatively rapidly, fosters innovation, and represents the leading edge of psychiatric classification.

PURPOSE OF *ICD-9-CM*

In contrast to *DSM*, *ICD* is a statistical classification. It is intended to include every term that might be encountered in medical records, since its primary functions are the classification of morbidity for the indexing of medical records, medical care review, and basic health statistics (*ICD-9-CM*, p. xvii). It is in no sense a medical nomenclature (*ICD-8*, p. vii). As is appropriate for a standard statistical system, the *ICD* changes relatively slowly and within more narrow boundaries. In any translation between these two systems, the challenge is to achieve a compromise between the standard statistical reporting system and a nosological system.

LEVELS OF COMPATIBILITY

One level of compatibility between two systems is whether the code numbers are the same for similar categories (code compatibility). Here, *DSM-III-R* is a definite improvement over *DSM-III* (see table 1). All basic *DSM-III-R* code numbers are valid *ICD-9-CM* codes. Another level of compatibility is whether the terminology (or "rubric") in two systems is the same, given the same code number in the two systems (rubric compatibility). The terminology used in both *DSM-III-R* and *DSM-III* is in some cases different from that of *ICD-9-CM*, but as has been previously shown (5, 6), the *DSM-III/ICD-9-CM* terminology is usually equivalent, and this remains the case for *DSM-III-R*. For example, organic affective syndrome (*ICD-9-CM*) is equivalent to organic mood disorder (*DSM-III-R*).

TABLE 1. Code, Rubric, and Case Incompatibilities Between *DSM-III* or *DSM-III-R* and *ICD-9-CM*[a]

	DSM-III to *ICD-9-CM*		*DSM-III-R* to *ICD-9-CM*	
Incompatibility	N	%	N	%
Code				
Additional zeros	62	17.1	55	21.2
Other	49	13.5	8	3.1
Rubric	14	3.9	7	2.7
Case	0	0.0	7	2.7
Total	125	34.5	77	29.7
Other than additional zeros	63	17.4	22	8.5

[a]Each code counted only once. There are 362 *DSM-III* codes and 259 *DSM-III-R* codes.

However, the most important test of the compatibility of two systems is whether the same clinical cases are included in a single category in both systems, whether or not the categories differ by code number or terminology (case compatibility). That is, given that a group of cases is placed in one category in a system, can an analogous category be found in the other system which will also contain those cases? *DSM-III* contained no such incompatibilities (table 1), but several were introduced into *DSM-III-R*.

The direction of the translation is also important in determining case compatibility. A group of cases in system A may fit completely into an analogous category in system B, allowing for a crosswalk from A to B. However, if the category in system B is more inclusive, a translation from B to A may not be possible. An example is the *DSM-III-R* category of panic *disorder* with agoraphobia and the *ICD-9-CM* category agoraphobia with panic *attacks* (code 300.21). The *ICD-9-CM* category is more inclusive than the *DSM-III-R* category but would include all of the *DSM-III-R* cases, since a patient has to have panic attacks in order to have panic disorder. The reverse crosswalk, from *ICD-9-CM* to *DSM-III-R*, however, is, strictly speaking, not possible, since *ICD-9-CM* contains cases that *DSM-III-R* would not consider as cases (i.e., *ICD-9-CM* does not require multiple attacks or impose a time constraint).

If a two-way translation is required, cases in analogous categories of the two systems must be identical. One cannot be more inclusive than the other. This is, in fact, true of most categories in *DSM-III-R* compared to *ICD-9-CM* (e.g., 295.32, schizophrenic disorder, paranoid type, chronic, is completely analogous in the two systems).

Code Compatibility

We found few code incompatibilities between *DSM-III-R* and *ICD-9-CM* that did not also represent rubric or case incompatibility. One example, however, is code 780.54 in *DSM-III-R* (hypersomnia with no known organic etiology). The correct crosswalk is to *ICD-9-CM* code 307.44 (persistent disorder of initiating or maintaining wakefulness). This is because the 780 series in *ICD-9-CM* contains cases with an organic etiology, while the 307 series in *ICD-9-CM* contains cases with *no* organic etiology. *DSM-III-R* clearly states that there is no known organic etiology, so the *DSM-III-R* 780.54 categorization is an error in code number. This is not case incompatibility, since the cases in *DSM-III-R* would be completely contained in the *ICD-9-CM* category.

Rubric Compatibility

A problem of rubric compatibility occurs when the terminology used in the two systems does not appear to be analogous. Such a problem arises in the use of the term "Alzheimer's." *ICD-9-CM* uses the Alzheimer's rubric for only presenile dementia (290.1x), while *DSM-III-R* includes Alzheimer's as part of the terminology for both presenile and senile dementia (290.0x–290.3x). The reason is that evidence indicates that the pathology for the senile and presenile conditions is the same and is of the Alzheimer type (8). This may cause confusion in coding, since "Alzheimer's" in the *ICD-9-CM* index volume leads the *ICD-9-CM* coder to only presenile dementia. The controlling rubric, however, is senile/presenile, rather than the Alzheimer's designation. We view this as only rubric incompatibility because there is no alternative category in *ICD-9-CM* for senile dementia of the Alzheimer's type.

Another example of a problem of rubric compatibility is code 302.85, gender identity disorder of adolescent or adult life. *DSM-III-R* adds "nontranssexual type," and this may lead to confusion as to where the disorder should be placed in *ICD-9-CM*, since there is no such specific rubric in *ICD-9-CM*. However, since the primary category is gender identity disorder, rather than transsexualism, the translation to 302.85 in *ICD-9-CM* is clear.

A more complicated example of incompatibility at the rubric level is found in the sleep disorder section of *DSM-III-R*. Code 307.40 contains a rubric unique to *DSM-III-R*—dyssomnia. It has the meaning of any insomnia, hypersomnia, or disorder of the sleep-wake cycle (*DSM-III-R*, page 298). If one assumes that the *DSM-III-R* definition of dyssomnias not otherwise specified includes all unspecified nonorganic sleep disorders (the *ICD-9-CM* rubric for 307.40), then the *DSM-III-R* category of dyssomnias not otherwise specified is indeed analogous to 307.40 in *ICD-9-CM*, and the only incompatibility would be rubric incompatibility. In any translation between systems, an assessment must be made as to the reasonableness of such assumptions. In this instance, as well as others, we judged that the assumptions being made were indeed reasonable.

Case Compatibility

Incompatibility at the case level occurs when there is a high likelihood that a group of cases in one system would be placed in a category in the second system that does not share a common code number or rubric. An example of incompatibility at the case level is code 307.40 in *DSM-III-R*, which (in addition to using the rubric of dyssomnias not otherwise specified, as noted earlier) uses the rubric of parasomnias not otherwise specified.

Unfortunately, the crosswalk is not valid between parasomnia of nonorganic origin (the intent of *DSM-III-R*) and code 307.40 in *ICD-9-CM*, but there is a valid crosswalk between it and code 307.47, as per the *ICD-9-CM* index. The cases in 307.40 in *DSM-III-R* (parasomnias and dyssomnias not otherwise specified) therefore are divided between two categories in *ICD-9-CM* (307.40 and 307.47). There is case incompatibility in translations from *DSM-III-R* to *ICD-9-CM*. There is no case incompatibility in the *ICD-9-CM* to *DSM-III-R* direction, however, since both *ICD-9-CM* categories of parasomnias not otherwise specified (307.47) and nonorganic sleep disorders, unspecified (307.40), fit neatly into the 307.40 category of *DSM-III-R*.

A similar example of case incompatibility in the *DSM-III-R* sleep disorders section is 780.50 (hypersomnia or insomnia related to a known organic factor). The closest *ICD-9-CM* categories are 780.54 and 780.52, which are separate categories for hypersomnia and insomnia.

Other case incompatibilities arise from the *DSM-III-R* use of the term not otherwise specified. This terminology means that within the broad category in question, there is no specification whatsoever to guide placement. For example, a chart diagnosis of eating disorder could not be placed into the bulimia, anorexia nervosa, or pica categories and would have to be coded to the unspecified eating disorder category (i.e., the type of eating disorder is not specified). In *ICD-9-CM* the term not otherwise specified is equivalent to the term unspecified (p. xxiii).

"Unspecified" is different from "other, specified" and just "other," which mean that a specific entity is named but cannot be placed into another category in *ICD-9-CM*. For example, in *ICD-9-CM* process schizophrenia would be coded to the 295.8x category (other specified types of schizophrenia), rather than to the unspecified category (295.9x), since "process" specifies a type of schizophrenia. Schizophrenia without modification would code to 295.9x in *ICD-9-CM*.

However, in *DSM-III-R*, the terms not otherwise specified and other, specified, are confused in some instances, with the same code in *DSM-III-R* representing both categories. For example, 315.90 in *DSM-III-R*, which codes both developmental disorder not otherwise specified and specific developmental disorder not otherwise specified, contains the contents of both *ICD-9-CM* 315.8, other specified delays in development, and 315.9, unspecified delay in development. Indeed, the *DSM-III-R* rubric is internally contradictory, since the terms specific and not otherwise specified (i.e., unspecified) are both used. This is a case incompatibility in a *DSM-III-R* to *ICD-9-CM* translation but not necessarily in an *ICD-9-CM* to *DSM-III-R* translation, since both *ICD-9-CM* categories would be included in the single *DSM-III-R* category. (In the crosswalk, *DSM-III-R* 315.90, specific developmental disorder not otherwise specified, was translated to *ICD-9-CM* 315.90 by taking "not otherwise specified" in *DSM-III-R* as the controlling rubric, rather than "specific.")

DIFFERENCES IN FORMATTING

Two problems in *DSM-III-R/ICD-9-CM* compatibility are seen by the developers of *DSM-III-R* as simply differences in style or format. The first is the presence in *DSM-III-R* of fourth- and fifth-digit zeros that are not found in *ICD-9-CM* (e.g., 316 in *ICD-9-CM* becomes 316.00 in *DSM-III-R*). These extra zeros are very troubling to medical records administrators and computer programers, who are used to each digit having content (i.e., having a specific meaning). In *DSM-III-R*, however, these are nonsubstantive zeros and have no content. They are there to make all *DSM-III-R* codes five-digit codes and do not affect the crosswalk to *ICD-9-CM*. To medical records and computer personnel, however, this represents code incompatibility. The practical importance of this is that codes with these extra zeros are routinely rejected as invalid by some third-party payers and by some agencies who collect statistics, since they accept only *exact* *ICD-9-CM* codes.

Second, in some instances a single *DSM-III-R* code is used for several diagnostic categories. For example, in *DSM-III-R* code 304.50 is used both for hallucinogen and phencyclidine (PCP) dependence. *ICD-9-CM* includes both of these categories under a single code number (PCP is included in the index), whereas *DSM-III-R* lists the two categories separately and repeats the code number. The effect in the two systems is the same (i.e., both PCP and hallucinogen dependence are coded to 304.50). Another example is 307.46, which in *DSM-III-R* is used both for sleep terror disorder and sleepwalking disorder, whereas *ICD-9-CM* lists the code only once as somnambulism or night terrors. The practical importance of this is that it gives *DSM-III-R* the appearance of being different from *ICD-9-CM*. Some facilities have rejected the use of *DSM-III-R* on the grounds that it is incompatible with *ICD-9-CM*, largely on the basis of these differences in appearance.

This and the previous example illustrate the greater specificity usually found in a nosology, when compared to a statistical system. The need in a nosological system is to define categories as narrowly as possible so as to arrive at groupings that are clinically useful. A statistical system, however, must remain broad in its classifications so as to allow each patient to be coded somewhere in the system, whether or not diagnostic criteria are met.

CONCLUSIONS

Although there are various compatibility problems between *DSM-III-R* and *ICD-9-CM*, most of them are minor and can be managed through use of the crosswalk. Differences in code number or rubric are not in themselves a problem in translating between systems; however, such differences are not trivial, since they could lead some clinical facilities to reject the use of *DSM-III-R* because of the appearance of incompatibility with *ICD-9-CM*.

From a technical point of view, however, the only real difficulties in a crosswalk occur when a single category in one system contains cases that do not fit into a single category in the other system. Of the 259 codes in *DSM-III-R*, only seven categories (3%) were problematic at a case level in a crosswalk from *DSM-III-R* to *ICD-9-CM*, and none of the problems precluded a workable crosswalk. When there were differences, they were not of such magnitude as to be important for purposes of medical record indexing or vital statistics reporting. They were also not of such magnitude as to affect the use of *DSM* and *ICD* in clinical practice. For these uses, the *DSM-III-R* codes we have identified as having case compatibility problems can be thought of as analogous to *ICD-9-CM* categories. In addition, most of these problem codes are probably little used, although data are not available to confirm this. It is only with regard to clinical or nosological research that fine distinctions between the two systems become important. But for nonresearch uses, we found no situations in which reconciliation between the two systems was impossible. (A table listing instances in which there is a question as to case compatibility between *DSM-III-R* and *ICD-9-CM* is available from the APA Office of Research.)

In an evaluation of the differences between systems, it is important to remember the differences between a nosology and a statistical classification and that the content of *ICD-9-CM* categories is not spelled out by the use of criteria, but rather by a glossary and an index that are meant for the placement of medical terms, rather than for the formulation of a specific diagnosis. This means that microcomparisons between *DSM* and *ICD* for clinical or nosological research purposes are very difficult. Case by case examination is really needed for such uses, rather than the comparison

TABLE 2. Advantages of *DSM-III-R* and *ICD-9-CM* to Various User Groups

User Group	*DSM-III-R*	*ICD-9-CM*
Clinicians	Presence of diagnostic criteria; standard for clinical psychiatry; more quickly integrates results of research; includes only clinically relevant codes; multiaxial	Submission to third parties who require *ICD-9-CM;* international standard (for relating to colleagues in other countries)
Medical records administrators	Used by records rooms in many psychiatric facilities; uniformly used by clinicians in all psychiatric facilities	Used by records rooms in all nonpsychiatric medical and some psychiatric facilities; used by clinicians in nonpsychiatric medical facilities; lengthy, complete index; contains most terms found in medical records; no need for translation to submit to third-party payers or federal agencies
Researchers	Used for much psychiatric research; diagnostic criteria yield more standardized instruments; more quickly integrates results of research	Used in most nonpsychiatric medical research; can be directly compared with other medical databases in the United States and internationally; changes more slowly and within more narrow boundaries

of nonresearch databases (although such databases may be quite useful for services or policy research). (A more detailed comparison of *DSM-III-R* and *ICD-9-CM*, meant to assist researchers, is available from the APA Office of Research.)

Therefore, whether one chooses to use *DSM* or *ICD* (or both) depends on the goals of the user (table 2). For example, the clinician who is working with a patient is much better off with *DSM*, since it is intended to classify patients in ways that are meaningful for evaluation, treatment, and determination of prognosis. That same clinician, however, may find a translation to *ICD* useful in submitting insurance claims. It would be beneficial to scientifically study the optimal uses of these two systems, but unfortunately, such research has not been forthcoming.

Dealing with the differences between *DSM-III-R* and *ICD-9-CM* need not be a difficult task. The crosswalk itself is one useful resource. In addition, the extra zeros in *DSM-III-R* could be suppressed automatically in computerized databases, yielding the exact *ICD-9-CM* codes. Rubric incompatibilities could be dealt with by publishing an extensive index of *DSM-III-R* terms, each of which would be cross-referenced to the analogous term in *ICD-9-CM*. (This would be of great help in medical records coding.) As noted, *DSM-III-R/ICD-9-CM* case incompatibilities are infrequent and will seldom affect the work of clinicians or medical records administrators, but these personnel should always be alert to the implications in using codes where there is a question as to case incompatibility.

ICD-10 and *DSM-IV* are currently in development, and efforts are being made to ensure even greater compatibility. The two systems need not be (and, in fact, could not be) identical, but efforts at achieving maximum compatibility are essential. For example, similarities between *DSM-IV* and *ICD-10* could be maximized by arranging the documents in similar ways, using similar terminology and definitions so that the nosological system is essentially a subset of the statistical classification (one of a family of classifications, with *ICD* as the single parent), using identical coding schemes and code numbers, following similar overall procedures (e.g., multiaxial systems), and designing a standard system for linkage.

Such efforts toward compatibility are vital. Without such compatibility, nosology would have no standard statistical reference point from which to innovate, and nosological systems developed by various groups would be so different as to be useless in clinical or scientific communication. Similarly, without close links to nosology, statistics would change too slowly, becoming over the years irrelevant to the clinical and research world. Efforts to achieve compatibility need to be made as *ICD-10* and *DSM-IV* are developed, not after the documents are published. This examination must involve many parties, including those familiar with the detail of *ICD* and *DSM*, as well as clinical and research psychiatrists, psychiatric nosologists, and medical records administrators.

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Sex Differences in Olfactory Function in Schizophrenia

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Olfactory identification and olfactory acuity were measured in 41 schizophrenic patients receiving neuroleptic medication and in 43 normal control subjects. The performance of the male schizophrenic patients was significantly lower than that of the female patients and the male and female normal control subjects. The last three subgroups performed at equivalent levels. These findings are discussed with respect to other reported sex differences in schizophrenia, including frequency of specific neurological signs and structural brain abnormalities, response to neuroleptic medication, and long-term outcome. The findings suggest that the sex of the patient may be a critical variable in understanding the processes of schizophrenia.

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In a previous study (1), we found that patients with schizophrenia had deficiencies in the ability to identify odors. These deficiencies were not related to dopamine blockade, since psychiatric patients without the diagnosis of schizophrenia who were taking neuroleptic medication performed as well as normal subjects. Similarly, test performance was not related to level of overt psychopathology, exposure to or duration of neuroleptic therapy, or other nuisance variables such as smoking. It was observed that this olfactory deficiency was confined to the male patients with schizophrenia. However, the number of female subjects in the initial study was limited to three. Therefore, the purpose of the current study was to replicate the original study and ascertain if there truly is a sex difference in the ability of patients with schizophrenia to identify odors. Confirmation of this observation would be consistent with other studies (2–5) that have found differences between male and female schizophrenic patients in frequency of specific neurological signs and structural brain abnormalities, response to neuroleptic medications, and long-term outcome.

With the upsurge of scientific interest in olfaction, the pertinent neuroanatomical pathways have been better delineated and hypotheses have been put forward concerning functional specialization of specific cortical regions. A number of studies (6, 7) have shown that olfactory acuity and identification are separate and, to a degree, independent functions. For example, subjects with normal acuity have been shown to have deficiencies in identification of different odors (8). Such a dissociation of olfactory functions has been reported for patients with Korsakoff's syndrome (9) and for patients with frontal lobe lesions—in particular, lesions involving the orbital frontal cortex (7, 10). The findings for patients with Korsakoff's syndrome complement the finding on the orbital frontal cortex because of the high number of axonal projections between the dorsal medial nucleus of the thalamus and the orbital frontal cortex. Given the historic and ongoing speculation regarding the role of the frontal cortex in schizophrenia (11–14), the examination of olfactory identification may provide a simple behavioral assessment of orbital frontal function. Moreover, unlike many tests of frontal cortex function, the assessment of olfactory identification does not depend on higher cortical functions such as abstraction.

In the current study, we used the Pennsylvania Smell Identification Test (8) to examine the ability of male and female patients with schizophrenia and of normal control subjects to identify various odors. Olfactory acuity was assessed in a subsample of the schizophrenic patients by using stepwise serial dilutions of *n*-butyl alcohol (10). This procedure was done to ensure that olfactory deficiencies were not a result of impaired acuity, although it has previously been shown that olfactory acuity is normal or perhaps heightened in patients with schizophrenia (15, 16).

METHOD

The Pennsylvania Smell Identification Test (8) was administered to four groups: 26 men with schizophrenia, 15 women with schizophrenia, 23 normal men, and 20 normal women. The mean ages of the groups (26.3, 25.3, 29.6, and 29.6 years, respectively; range=18–54) were not significantly different (F=1.17, df=3, 90, p<0.32). Given the known effects of aging on olfactory function, the fact that the normal men and women were slightly older than the male and female schizophrenic patients makes it unlikely that age had

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any effects on the analyses. The percentage of smokers was low in the normal groups (13%, N=3, of the men and 10%, N=2, of the women) and comparatively higher in the schizophrenic groups (58%, N=15, of the men and 67%, N=10, of the women). The normal subjects were volunteers from the hospital and university community. No subject was excluded from this group on the basis of his or her smell identification test score. All subjects gave informed consent, and the study was approved by the University of British Columbia Human Research Committee.

The diagnosis of schizophrenia was made by two independent psychiatrists, and all patients met the *DSM-III* and *ICD-9* criteria for this diagnosis. In addition, a Global Assessment Scale (GAS) (17) rating was given to each patient. The male and female patients did not differ on this variable (for the men, mean±SD GAS score=39.8±8.6; for the women, 42.9±8.7; $t=-1.09$, df=39, $p\leq 0.28$). At the time of testing, all patients were receiving maintenance neuroleptic therapy and no subject was in remission. Within 3 months of testing, all patients were given physical examinations and the following laboratory investigations were conducted: CBC with differentials, urinalysis, ECG, chest X-ray, and determination of T_4 levels. In addition, any patient whose score on the smell identification test was not in the normal range of the standardization sample was examined by a neurologist (T.A.H.) and a serum zinc level was obtained. The purpose of these examinations was to identify and exclude any patient whose poor score could be accounted for by other factors, such as upper respiratory tract infection, persistent rhinitis, nasal cocaine use, head injury, facial trauma, or other specific medical conditions (e.g., hypothyroidism).

The Pennsylvania Smell Identification Test has 40 items. Each item consists of a card with a scent-impregnated area that is activated by scratching. Above this area are four potential responses for identifying the odor (e.g., lilac, chili, coconut, and whiskey). Each subject was tested individually to ensure comprehension of the task and compliance with the instructions. Each subject was asked to sniff the scratched impregnated area and then tell the examiner the correct response from the four alternatives on the card. If the subject could not initially identify the scent, the procedure was repeated until one of the four alternatives was chosen. Examiners were blind to the correct responses. All subjects performed the task within 8–25 minutes.

Olfactory acuity (odor detection threshold) was determined by having the subjects smell solutions of increasing concentrations of *n*-butyl alcohol in distilled water. There were 10 concentrations ranging from 1×10^{-5} M to 2 M. We selected *n*-butyl alcohol because it has been found to stimulate only the first (olfactory) cranial nerve and not the fifth (trigeminal) (10, 18, 19). The dilutions were made up in test tubes (height=12 cm, internal diameter=1.2 cm) and filled with 6 mm of liquid. Each test tube containing odorant was presented along with a test tube containing only distilled water in a forced-choice paradigm. The subjects were asked to sniff each of the two test tubes and indicate which smelled stronger. When a correct or incorrect choice was made, the next weaker or stronger concentration was presented until the threshold was determined. Threshold was defined as four consecutive correct responses with chance performance for the next weaker concentration. The test was administered to both nostrils. The intertrial interval was approximately 15 seconds, and the test was administered in as odorless an environment as possible. Fourteen of the male schizophrenic patients and nine of the female patients took the test.

TABLE 1. Pennsylvania Smell Identification Test Scores of 41 Schizophrenic Patients and 43 Normal Control Subjects

Group	Test Score[a] Mean	SD	Range
Normal control subjects			
Female (N=20)	37.8	1.6	35–40
Male (N=23)	37.1	1.2	34–39
Schizophrenic patients			
Female (N=15)	36.1	1.6	34–40
Male (N=26)	33.8	5.2	20–39

[a]Highest possible score=40.

RESULTS

The means, standard deviations, and ranges of the smell identification test scores for the four groups are presented in table 1. A two-way analysis of variance yielded a significant Group by Sex interaction (F=4.62, df=1, 80, $p\leq 0.05$), and a post hoc Tukey's honestly significant difference test indicated that the performance of the schizophrenic men was significantly worse than that of the other three groups ($p<0.05$), which did not differ significantly. With respect to functional appraisal, using a liberal criterion for normal sense of smell (score≥35) based on standardization data in the smell identification test manual (8), we found that 100% of the 20 female control subjects and 96% (N=22) of the 23 male control subjects would be classified as normal, whereas 93% (N=14) of the female schizophrenic patients and only 58% (N=15) of the male patients would be classified as having a normal sense of smell. These data clearly indicate that the olfactory deficiencies in odor identification were confined to a considerable proportion of the male patients with schizophrenia.

For the subsamples of male and female schizophrenic patients in whom olfactory acuity testing was done, the levels of acuity for the two sexes were not significantly different: for the women, the mean±SD score was 5.00±1.12; for the men, 5.79±1.66 (F=1.85, df=1, 21, n.s.). (The ability to detect an odor in a 2.4×10^{-2} M concentration results in a score of 6; 8.1×10^{-3} M concentration results in a score of 5.) In fact, the males had slightly better acuity scores. In contrast, there was still a significant difference between the male and female patients on the smell identification test (for the men, the mean±SD score=32.4±6.16; for the women, 37.4±1.59; $F=5.63$, $df=1, 21$, $p \leq 0.05$), and the overall level of performance for the subsamples was almost identical to that of the respective full samples. The olfactory acuity testing indicated that lack of acuity could not account for the poor performance in odor identification by the male schizophrenic patients.

DISCUSSION

The findings of this study suggest that the previously reported deficiency in olfactory identification in patients with schizophrenia is unique to male patients and cannot be accounted for by lack of olfactory acuity. Besides replicating our earlier findings for male patients, the sex difference in performance is striking. First, of the 18 female patients assessed in the two studies, only one could be classified as having a deficient sense of smell (smell identification test score= 34), whereas of the 38 male patients assessed, 20 (53%) could be classified as anosmic or having a deficient sense of smell. Given the simplicity of the smell identification test in terms of task demands and the equivalent performance of the male and female patients on the test of olfactory acuity, either neuroanatomical or biochemical hypotheses may be the most probable explanations of this deficiency in olfactory identification.

In this regard, there is a growing body of literature suggesting that male and female schizophrenic patients do differ on a number of pertinent variables. For example, using cranial CT images, Johnstone et al. (20) found that enlargement of the paired lateral ventricles in patients with schizophrenia was confined to male patients. Subsequently, Shelton et al. (21) found that enlargement of the third ventricle was more pronounced in male schizophrenic patients than in female schizophrenic patients. Andreasen et al. (2), using magnetic resonance imaging, found that reductions in the volume of the prefrontal cortex were more prevalent in male than in female schizophrenic patients. In a recent report on post-mortem studies of patients' brains, Falkai et al. (22) found reductions of volume in the entorhinal cortex in schizophrenic patients. Although the sample sizes were small (two male and 11 female patients, seven male and four female control subjects), it was clear that the reduction was two to three times greater in the male patients. Moreover, none of these patients had ever been treated with neuroleptic medication. With respect to the findings in the current study, these data and the data implicating the orbital frontal cortex in odor identification suggest that the medial temporal cortex and the orbital frontal cortex may be involved in the schizophrenic process in a subsample of male patients.

More generally, there have been reports of sex differences in prevalence of neurological signs (5), response to neuroleptic therapy (3), and premorbid as well as long-term social adjustment (4). As with the neuroanatomical variables, a higher degree of pathology or maladjustment has been found in male patients. Our finding of a deficit on a relatively primitive sensory identification task in a subsample of male schizophrenic patients, coupled with those we have just mentioned, suggest that sex may be a critical variable in schizophrenia in terms of etiology and perhaps in terms of treatment.

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A Basic Residency Curriculum Concerning the Chronically Mentally Ill

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In this paper a group of knowledgeable individuals with expertise in psychiatric education present their recommendations for a basic psychiatric residency curriculum concerning the chronically mentally ill. The proposed curriculum consists of knowledge, skill, and attitude educational objectives, as well as clinical experiences, faculty supervision, didactics and seminars, and evaluation mechanisms. Recommendations are also made concerning changes in the Accreditation Council for Graduate Medical Education's Special Requirements for Residency Training in Psychiatry, which would require residency programs to place more emphasis on training to meet the needs of the chronically mentally ill. Obstacles to the implementation of the proposed recommendations are presented and possible solutions are discussed.

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Since the President's Commission on Mental Health in the late 1970s (1), a great deal of attention has been focused on the care and treatment of the chronically mentally ill. It has become apparent that this group of patients are very diverse and that their needs are complex (2, 3). For mental health care providers to supply adequate service to these patients requires knowledge about chronic mental illness as well as complicated service delivery systems, skill in working with a patient's entire biopsychosocial network, and an attitude that conveys hope and dedication to the task (4). One important and vexing aspect of this issue has been the lack of well-trained psychiatrists to serve this patient population (5, 6). Academic departments of psychiatry have been encouraged to increase the involvement of their trainees in the public service delivery system of community mental health programs and state hospitals (7–9). Several programs around the country have been proposed as models of how this collaboration might be done (10, 11). A number of psychiatric residency programs have described how they provide their residents with the knowledge, skills, and attitudes required to become specialists in meeting the needs of the chronically mentally ill (12, 13), and Nielson et al. (14) have suggested a comprehensive curriculum for training in this area. Despite all this laudable effort, it is apparent that a few departments of psychiatry with special programs and curricula will not be able to train sufficient numbers of psychiatrists to meet the pressing need that exists (15). Additional attention must be paid to the training of all psychiatrists in every program. To do so, however, requires the development of a basic core curriculum concerning the chronically mentally ill. Just what is it that every

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psychiatrist should be expected to know and be able to do with respect to the chronically mentally ill?

Representatives of the Alliance for the Mentally Ill (H.L.), the American Association of Chairmen of Departments of Psychiatry (J.H.S.), the American Association of Community Psychiatrists (C.R.G.), the American Association of Directors of Psychiatric Residency Training's Curriculum Committee (R.M.F., L.R.F., S.R.S., A.T.), APA's Committees on the Chronically Mentally Ill (D.L.C., S.M.G., D.D.K., H.R.L.) and Graduate Education (J.H.S.), and the Group for the Advancement of Psychiatry (H.R.L., K.M.) met during 1987 and 1988 to develop such a basic curriculum. In this paper, we will describe the results of those deliberations. We begin with an elucidation of several guiding principles that served as the foundation for the process and the recommendations that are made. We then present the proposed curriculum of educational objectives, clinical experiences, faculty supervision, and didactics and seminars as well as recommendations for evaluation. We suggest changes in the Accreditation Council for Graduate Medical Education's Special Requirements for Residency Training in Psychiatry (16) that would require programs to place more emphasis on training residents to serve the chronically mentally ill, and we conclude with a brief discussion of the obstacles to implementation of our recommendations and suggest strategies that might help overcome them.

GUIDING PRINCIPLES

To understand a process such as the one we are describing requires an appreciation for the principles that have served as its philosophical foundation. To a great extent, those principles will determine the outcome of the process. Several key concepts were important to our efforts to develop a basic residency curriculum concerning the chronically mentally ill.

First, it is crucial to be as specific as possible about the definition of chronic mental illness so that educational programs will train their residents to serve appropriate patient populations. Defining chronic mental illness is an elusive and somewhat controversial task, but we agree with those authorities who believe the definition should include criteria for duration and disability as well as for diagnoses (17). We believe the diagnoses should include *DSM-III-R*'s categories of organic mental disorders, schizophrenia, delusional disorders, psychotic disorders not elsewhere classified, and mood disorders, as well as certain severe and chronic personality disorders and psychoactive substance use disorders. The duration of illness should be long-term or indefinite, and the disability should be severe enough to interfere significantly with role performance (18, 19). For us, then, chronic mental illness is defined as a major mental disorder that is long-term or of indefinite duration and that interferes significantly with role performance.

Second, chronic mental illness is an important issue for modern medicine and psychiatry, and the understanding and treatment of the chronically mentally ill should be taught as such to all psychiatric residents. To be most effective, this education should incorporate information from the latest research and be taught by psychiatrists who are knowledgeable about chronic mental illness and who occupy positions of importance and prestige within academic psychiatry departments.

Third, chronic mental illness is similar in many ways to other chronic medical conditions; and providing care to the chronically mentally ill can be just as professionally rewarding and personally gratifying as serving other patients with chronic conditions if psychiatrists approach the task with the proper attitude, if effective treatment techniques are learned, and if working conditions are structured appropriately.

Fourth, the development of an effective collaborative relationship with chronically mentally ill patients, their families, and other providers and agencies that serve them is crucial to the understanding and treatment of chronic mental illness.

Fifth, a significant positive impact on psychiatric resident education concerning the chronically mentally ill can be achieved by incorporating modest changes of structure, process, and attitude into existing programs. A revolutionary overhaul of the entire educational system is neither necessary nor appropriate.

Sixth, to make our recommendations operational will require a broad-based educational and lobbying approach that addresses, in a systematic fashion, the concerns of residents, faculty, residency training directors, and chairmen.

The next two sections present the specific educational objectives, clinical experiences, faculty supervision, and didactics and seminars in our proposed basic curriculum.

EDUCATIONAL OBJECTIVES

We recommend that by the end of their residency training program, all residents have acquired the following knowledge, skill, and attitude objectives concerning the chronically mentally ill.

Knowledge and skills. Residents should demonstrate, by their knowledge and clinical ability, an understanding of 1) the characteristics and current status of their patients' lives, both inside and outside the clinical setting; 2) the impact of cultural, ethnic, and racial factors on themselves as well as their patients; 3) how to perform comprehensive biopsychosocial functional assessments that lead to diagnoses, problem lists, and individual treatment plans; and 4) realistic treatment strategies that include attention to primary care needs, crisis intervention, psychotherapy (individual, group, and family), pharmacotherapy, somatotherapy, psychosocial rehabilitation techniques, education of patients and families, and collaborative treatment planning with families and other service providers.

Attitudes. Residents should demonstrate by their attitude and behavior that they are appropriately 1) respectful and accepting of patients, their families, and other service providers; 2) sensitive to the experiential world of patients and their families; 3) positive and hopeful with respect to treatment and rehabilitation; 4) flexible in their approach to working with patients and their families; 5) aware of the value of a comprehensive and longitudinal approach to treatment; and 6) interested in the practical clinical application of current research findings to treatment.

CLINICAL EXPERIENCES, FACULTY SUPERVISION, AND DIDACTICS AND SEMINARS

To meet these basic educational objectives, we recommend that every residency training program incorporate the following clinical experiences, faculty supervision, and didactics and seminars.

Clinical experiences. 1) Every resident must follow closely a group of chronically mentally ill patients for at least 1 year beginning as early as possible in residency training. This 1-year period should bridge at least 2 years of the training program. The patients must include at least two for whom the resident is required to manage medications, as well as collaborate with another mental health professional who also works with the patients, and at least two for whom the resident provides more than just medication management. With respect to the last two patients, at least one must be treated with medication, at least one must require work with the patient's family, at least one must require contact with other service agencies, at least one must have been referred from a hospital to the resident for treatment, and at least one must have been referred from a nonhospital program. 2) For at least 1 year of their training, residents must regularly attend at least one ongoing clinical case conference that deals with the chronically mentally ill. 3) Residents should have exposure to diverse service delivery settings that reflect the complex systems involved in the treatment of the chronically mentally ill.

Faculty supervision. Residents must receive regular supervision of their work with their group of chronically mentally ill patients. This supervision must be provided by qualified faculty who have experience working with the chronically mentally ill, who value their work, and who are able to help residents attain the knowledge, skill, and attitude objectives described earlier.

Didactics and seminars. At some time during their residency program, residents must attend didactic presentations and seminars pertaining to the chronically mentally ill that address biopsychosocial assessment theory and techniques; psychosocial network theory; the process of working with families; problem list development and treatment planning techniques; cultural, ethnic, and racial issues; primary care problems; crisis intervention; individual, family, and group therapy; pharmacotherapy; somatotherapy; psychosocial rehabilitation techniques; patient and family educational techniques; work with agencies, mental health professionals, nonmental health care providers, and volunteers; research; legal issues including civil commitment, confidentiality, criminality, competency, and guardianship; funding and reimbursement issues; and the role of the psychiatrist in the mental health service delivery system.

RESIDENT AND PROGRAM EVALUATION

We recommend that every residency training program include an evaluation component to determine whether or not its residents have met the previously discussed educational objectives concerning the chronically mentally ill. This evaluation component must be keyed to the specific knowledge, skill, and attitude educational objectives, and residents should receive both written and verbal feedback about their performance from their supervisors at regular intervals during their training program. In addition, residents should receive both cognitive and clinical examinations, with content that is pertinent to the chronically mentally ill, at least twice during their training program. The evaluation component must also give residents the opportunity to provide both written and verbal evaluations of their clinical experiences, faculty supervision, and didactics and seminars at regular intervals during their training program. Programs must demonstrate that they have taken steps to correct identified deficiencies in either resident performance or program structure and function.

RECOMMENDED CHANGES IN THE SPECIAL REQUIREMENTS OF THE ACCREDITATION COUNCIL FOR GRADUATE MEDICAL EDUCATION

The Special Requirements for Residency Training in Psychiatry of the Accreditation Council for Graduate Medical Education (16) include the knowledge, skill, and attitude objectives as well as the didactics, clinical experiences, and faculty supervision that are necessary for a residency program to be accredited. By design, these special requirements are fairly general in order to encourage programs to develop their own methods of residency education within the broad guidelines. Their content is far less specific than our recommended curriculum, and they contain very few requirements specifically directed to the chronically mentally ill. In fact, the word "chronic" is used only once in the special requirements. That occurs in the section pertaining to required clinical experiences (section II.C.3.b.), where it states: "Each resident must have major responsibility for the diagnosis and treatment of a reasonable number and adequate variety of patients with both acute and chronic illness representing the major psychotic and nonpsychotic categories of psychiatric illness."

To be in keeping with the general nature of the special requirements, we do not necessarily recommend that our proposed curriculum be incorporated as it is written here. Rather, we believe there are a number of more modest changes that could be made in the special requirements that would go a long way toward encouraging residency programs to place more emphasis on training their residents to serve the chronically mentally ill. Our specific recommendations are 1) to add another knowledge objective (special requirement section II.B.1.) that would require residents to have an understanding of the biological, psychological, social, cultural, ethnic, racial, family, and iatrogenic factors that affect the long-term course and treatment of psychiatric illness; 2) to supplement the current didactic curriculum requirements (special requirement section II.C.2.b.) so that they include topics pertinent to the chronically mentally ill; 3) to modify the current 1-year outpatient requirement (special requirement section II.C.3.c.(2)) so that the experience exposes residents to patients with illnesses of different chronicities, emphasizes a biopsychosocial approach to outpatient treatment, and includes at least some long-term treatment experiences with patients who are chronically mentally ill; 4) to change the current requirement for supervised responsibility in community mental health activities (special requirement section II.C.3.c.(7)) to emphasize that the community setting must be a nonhospital program that provides the resident with clinical experience in making appropriate social, community, and family interventions with chronically mentally ill patients and that the experience should also include a consultation with a community agency; and 5) to alter the current requirement for supervised clinical management of patients with alcoholism and drug abuse (special requirement section II.C.3.c.(10)) so that some of these patients must also have other major psychiatric disorders.

While these recommended changes in the special requirements do not contain all of our proposed curricular content, they do meet the spirit of its intent. They would help ensure that all psychiatrists have the training necessary to understand and treat chronically mentally ill patients. They are broad enough to encourage local programs to meet them in their own ways and basic enough so that they should not be a significant burden for any program to fulfill.

OBSTACLES AND STRATEGIES IN IMPLEMENTING RECOMMENDATIONS

There are several obstacles that stand in the way of implementing our proposed recommendations, but there also exist a number of strategies that might be effective in overcoming them. To accomplish our goals will require the support of residents, faculty, training directors, and department chairs, each of whom has his or her own concerns. For residents, the main issues are understanding the relevance of the educational material to their future careers and the assurance of a stimulating and excellent training experience. These issues can be addressed by well-structured and well-supervised clinical rotations that demonstrate the pervasiveness of chronic mental illness as well as the challenge and fulfillment of serving this patient population. A number of academic departments have been successful in developing these types of educational experiences (9, 10, 12, 13).

For faculty, a major question is whether or not their professional investment in the chronically mentally ill will be appropriately rewarded with commensurate academic recognition by department chairs and promotion and tenure committees. The answer to this question will probably be negative unless the faculty members involved employ the type of balanced approach to their careers that faculty in other areas of interest use. To attempt to rely solely on their talents as administrators, clinicians, or even teachers will probably not be enough. It will also be important to focus on research and other scholarly activities in order to obtain the desired amount of professional recognition. This type of diversified academic career with an emphasis on the chronically mentally ill has clearly been possible to achieve in a variety of settings around the country (9, 11).

For training directors, it is often difficult to consider the possibility of adding more to an already overburdened curriculum, when component faculty all believe they are receiving insufficient emphasis. This is the main reason that the thrust of our effort here is to propose a basic rather than a comprehensive curriculum. Many programs will be able to meet these guidelines with only a shift in the emphasis of what currently is being done, rather than the addition of major new curriculum content. To accommodate even minor changes will be difficult for some programs, however, and will require a considerable amount of educational and administrative support. Fortunately, the American Association of Directors of Psychiatric Residency Training already has a structure in place to help meet this need. Much of the annual meeting of this organization is devoted to small group workshops designed to help training directors develop and administer their residency programs. Most training directors attend these meetings, which could provide an effective format to disseminate ideas about how our proposed curriculum might be incorporated most efficiently into existing programs.

For department chairs, a main concern is how to obtain the resources required to support qualified faculty to teach and supervise residents in the area of the chronically mentally ill. Several academic departments have designed innovative ways to share faculty with public service settings at little cost (10, 11, 13). In the past, the National Institute of Mental Health (NIMH) provided limited faculty support to some academic departments to train psychiatrists to serve the chronically mentally ill, and a new NIMH initiative to support a small number of faculty scholars in areas such as schizophrenia, mood disorders, aging, and severely mentally disordered children and adolescents has been funded recently. Whether or not this federal funding will continue in the future is unknown, but it should be encouraged vigorously. This type of fiscal enticement can have a tremendous impact on academic departments and the design of residency training programs. It can also be a source of encouragement for young faculty to develop an academic interest in the chronically mentally ill.

A final obstacle to overcome is the complicated policy structure of existing large and complex professional psychiatric organizations, which at times results in the preservation of the status quo. This issue must be confronted in a direct and open manner. A political lobbying strategy will need to be developed to engender the support of these organizations if any attempt is to be made to change the Special Requirements for Residency Training in Psychiatry. The decision to initiate such a strategy, however, should await the response of the field to our recommended curriculum and special requirement changes.

In summary, we have outlined in this paper a basic curriculum to train psychiatric residents to serve the chronically mentally ill, and we have suggested modest changes in the Special Requirements for Residency Training in Psychiatry that we believe would encourage residency programs to place more emphasis on this important area of education. While we are aware of a number of real obstacles to the implementation of our proposals, we also believe that practical solutions are available. Their implementation could go a long way toward making our recommendations a reality.

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Obsessive-Compulsive Disorder: A Double-Blind, Placebo-Controlled Trial of Clomipramine in 27 Patients

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Clomipramine was significantly superior to placebo in a 10-week double-blind, placebo-controlled trial in 27 outpatients who met DSM-III-R *criteria for obsessive-compulsive disorder.*

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The most promising and well-studied drug that has been used in the treatment of obsessive-compulsive disorder is the tricyclic antidepressant clomipramine, which can now be obtained by special procedures in the United States from Ciba-Geigy Pharmaceutical Company but is available by prescription in Canada, Mexico, and Europe (1, 2). As part of a multicenter trial to further evaluate its effectiveness, we performed a placebo-controlled, double-blind trial of clomipramine in 30 well-characterized outpatients who met *DSM-III-R* criteria for obsessive-compulsive disorder.

METHOD

After giving informed consent and undergoing a drug-free period of at least 2 weeks and a 2-week single-blind placebo washout period, subjects were randomly assigned either to clomipramine or to identically appearing placebo capsules for a 10-week study period. Drug doses were initially titrated up to 200 mg daily, followed by a flexible dose schedule up to 300 mg daily (the maximum dose has since been lowered to 250 mg because of risk of seizures at higher doses).

Patients were assessed weekly on the Yale-Brown Obsessive-Compulsive Scale, which has been used as the main dependent variable in multicenter trials of clomipramine, sertraline, and fluvoxamine and has demonstrated reliability and validity (data and instrument available from Wayne Goodman, M.D., Yale University). Although interrater reliability was not assessed in the present study, all raters were trained by videotape instruction, and a separate study in our clinic yielded an intraclass correlation coefficient of 0.97 for the Yale-Brown scale. In addition, the National Institute of Mental Health (NIMH) obsessive-compulsive scale (3), the Hamilton Rating Scale for Depression (4), and a global assessment of obsessive-compulsive symptoms were administered.

RESULTS

Three patients stopped the study prematurely; two dropped out because of side effects (excessive sedation), and one was terminated for noncompliance with the appointment schedules. Other side effects included dizziness (drug, N=9; placebo, N=1), nausea (drug, N=1; placebo, N=0), sedation (drug, N=9; placebo, N=4), sexual dysfunction (drug, N=3; placebo, N=0), blurred vision (drug, N=2; placebo, N=2), tremor (drug, N=5; placebo, N=0), constipation (drug, N=2; placebo, N=2), forgetfulness (drug, N=2; placebo, N=0), headache (drug, N=2; placebo, N=3), increased sweating (drug, N=3; placebo, N=0), weight gain (drug, N=1; placebo, N=0), dry mouth (drug, N=10; placebo, N=2), and miscellaneous effects (drug, N=3; placebo, N=3).

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TABLE 1. Change in Obsessive-Compulsive and Depressive Symptoms of 27 Obsessive-Compulsive Patients Receiving Clomipramine or Placebo

	Score											
	Hamilton Rating Scale for Depression: Baseline		Global Assessment of Obsessive-Compulsive Symptoms: Week 10		Yale-Brown Obsessive-Compulsive Scale				NIMH Obsessive-Compulsive Scale			
					Baseline		Week 10		Baseline		Week 10	
Group	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Clomipramine (N=13)	5.3	2.5	1.9[a]	1.0	24.1	5.8	15.2[b]	5.2	9.7	1.6	5.8[c]	2.0
Placebo (N=14)	4.7	2.5	0.2	0.8	27.2	4.1	24.9	5.2	9.6	1.1	8.7	2.2

[a] Higher scores indicate more improvement; significantly higher than score for placebo group at week 10 (t=4.73, df=25, $p<0.001$, two-tailed test).

[b] Significantly lower than score for placebo group at week 10 (F=18.1, df=1, 36, $p<0.001$, two-tailed test).

[c] Significantly lower than score for placebo group at week 10 (F=13.4, df=1, 36, p=0.001, two-tailed test).

Data analyses were conducted on 13 patients in the drug group and 14 in the placebo group. The mean± SD age of the 27 patients who completed the entire 10-week study was 39.4±10.5 years; there was no significant difference between groups (t=1.59, df=25). Of the 27 patients, 13 were men and 14 were women, which was not a significant difference (χ^2=0.36, df=1). At baseline, groups did not differ significantly on Yale-Brown scale scores (t=1.28, df=25), NIMH scale scores (t=0.17, df=25), or Hamilton scale scores (t=0.54, df=25). Baseline data are summarized in table 1.

The two major dependent variables (the Yale-Brown and NIMH scale scores) were analyzed by two-factor analyses of variance (ANOVAs), with repeated measures on one factor (5). The ANOVAs had a between-group factor with two levels of treatments (drug versus placebo) and a repeated measures factor with 10 levels, one for each week of the study after baseline. One female patient in the placebo group was excluded from the ANOVAs due to missing data.

For Yale-Brown scale scores, ANOVA found a significant interaction effect (F=6.15, df=9, 216, $p<0.001$; Greenhouse-Geisser corrected $p<0.01$), indicating different patterns of change over time for the two groups. Because of the significant interaction effect, tests of simple main effects (5) were calculated for each week and tested with the Bonferroni correction method at a conservative p level of 0.005 (i.e., 0.05/10). These conservative tests found no significant differences between the two groups at week 1 through week 4; significant differences at all weeks from week 5 to week 10.

Improvement on the Yale-Brown scale was also assessed as the number of patients achieving various percentage improvements from baseline to week 10 in each group. In the clomipramine group, three patients improved 0%–19%, four improved 20%–39%, four 40%–59%, one 60%–79%, and one over 80%. In the placebo group, scores improved 0%–19% in 11 patients and 20%–39% in three patients; none improved 40% or more. These frequencies were not assessed by contingency table analysis due to low statistical power for this test.

For NIMH scale scores, ANOVA found a significant interaction effect (F=3.31, df=9, 216, $p<0.001$; Greenhouse-Geisser corrected $p<0.05$), indicating different patterns of change over time for the two groups. Because of the significant interaction effect, tests of simple main effects were computed for each week, as described earlier. These tests found no significant difference between the two groups at week 1 through week 4; significant differences were found at all weeks from week 5 to week 10, with the exception of week 7.

On this scale, with clomipramine, one patient improved 0%–19%, six 20%–39%, four 40%–59%, and two 60%–79%; none improved 80% or more. With placebo, scores improved 0%–19% in 10 patients and 20%–39% in three patients; none improved 40% or more, with the exception of one patient who improved 60%–79%. These frequencies were not assessed by contingency table analysis due to low statistical power for this test.

At week 10, mean global assessment scores were significantly higher for the drug group than for the placebo group (table 1).

DISCUSSION

What is the clinical significance of the statistically significant changes in this study? To illustrate, at week 10 the mean global improvement score was 1.9 (much improved) for the clomipramine group, compared to 0.2 (unchanged) for the placebo group. On the Yale-Brown scale, the score for the placebo group was essentially unchanged, while in the drug group, the score fell from approximately 24 to 15. Although 15 still represents the presence of a significant level of symptoms, patients undergoing such a change report that they are much better. On the NIMH scale, the drug group's score decreased from about 10 to about 6, again representing a drop from severe obsessive-compulsive behavior to subclinical symptoms. Taken together, these findings indicate that statistically significant improvements on these measures do, in fact, translate into clinical improvements. Patients are likely to improve further when given behavior therapy along with pharmacotherapy (1).

Clomipramine has been available in other countries for over a decade (1, 2). Following initial successes with intravenous clomipramine, uncontrolled trials with oral clomipramine yielded mixed results. Some reported little improvement, while others reported a good response. A few small controlled trials (see references 1, 2, 6 for reviews) have suggested that clomipramine is indeed an effective treatment for obsessive-compulsive disorder and is superior to both placebo and other tricyclics. The results of our study are consistent with these past results.

Consistent with earlier studies (7), a number of patients suffered side effects from clomipramine, but the dropout rate was rather low (10%). Since there is growing evidence that some of the newer serotonergic antidepressants, such as fluvoxamine, sertraline, and fluoxetine, may also be effective in the treatment of obsessive-compulsive disorder, we have a number of options for patients who do not respond well to initial drug treatment. Since fluoxetine is now available on the U.S. market and appears in initial studies to be effective (8, 9) and to have few side effects, it may be the initial drug of choice until clomipramine becomes more readily available.

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Benzodiazepine Use and Abuse by Patients at Outpatient Clinics

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The charts of 2,719 patients from several outpatient clinics were reviewed for evidence of use and abuse of benzodiazepines. According to the chart data and interviews with physicians, no patient met the criteria for benzodiazepine abuse or dependence.

(Am J Psychiatry 1989; 146:1331–1332)

There is concern that prescription of benzodiazepines may lead to undesirable consequences, particularly drug abuse. We surveyed the use of benzodiazepines in several outpatient clinics, psychiatric and nonpsychiatric, to determine whether such use leads to abuse.

Epidemiologic studies of use and dependence have not supported the view that benzodiazepines are used excessively or that dependence or abuse is common (1–4). However, there is widespread concern about benzodiazepine abuse, as reflected by the recent decision in New York to require that benzodiazepine prescription forms be filled out in triplicate; this was formerly required only for schedule II drugs. There is no doubt that benzodiazepine abuse and dependence do occur. The question we addressed in our survey was whether benzodiazepine use in outpatient clinics leads to, or is associated with, abuse or dependence.

METHOD

This survey was done at Elmhurst Hospital Center, a 600-bed municipal hospital in Queens, N.Y., affiliated with the Mount Sinai School of Medicine. We reviewed the records of the adult psychiatry, geriatric psychiatry, medical primary care, cardiology, neurology, spinal cord injury, and backache outpatient clinics at the center. The last two clinics were selected because it was thought that their patients might be prescribed benzodiazepines for the drugs' muscle relaxant properties.

We reviewed all the records of patients registered in the two psychiatric clinics and the spinal cord injury and backache clinics. In the other clinics, a predetermined number of charts were reviewed; all charts of patients who attended a clinic on the day the raters went to that clinic were rated until the predetermined number of charts had been reviewed.

This method of selection did not provide a random sample of all patients registered in these clinics, but it is unlikely that the sample was biased. If there was a bias, it might have been in favor of rating patients who were frequent clinic users, since patients with benzodiazepine abuse or dependence might be expected to go to a clinic more frequently.

Two raters (N.H. and L.A.) were responsible for chart review, and each chart was examined by both raters. If there was a disagreement left unresolved by discussion, the chart was reviewed by a senior staff psychiatrist (S.D. or B.K.). The chart assessment was conducted in stages. First, the note on the most recent clinic visit was read to see whether a benzodiazepine had been prescribed. If so, the chart notes for the previous 3 months were read in order to determine whether a threshold of at least moderate use had been reached; for patients 64 years old or younger, moderate use was defined as 15 mg/day of diazepam (or a comparable dose of another benzodiazepine) for at least 3 months. For patients over 64 years of age, the threshold dose was 7.5 mg/day (or its equivalent). If a patient met the criterion for the threshold dose, the chart was reviewed for any symptoms of substance abuse or dependence according to *DSM-III-R*, and the chart rater interviewed the patient's physician and completed a checklist of the symptoms of benzodiazepine abuse/dependence. A patient was considered to be an abuser or dependent if the chart review and physician interview revealed that the *DSM-III-R* criteria had been met.

RESULTS AND DISCUSSION

Table 1 illustrates our findings. Aside from the spinal cord injury clinic, where a third of the patients

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TABLE 1. Use and Abuse of Benzodiazepines by 2,719 Patients at Outpatient Clinics

Item	Psychiatry Clinic Patients				Medical Primary Care Clinic Patients				Cardiology Clinic Patients (N=100)		Neurology Clinic Patients (N=100)		Spinal Cord Injury Clinic Patients (N=43)		Backache Clinic Patients (N=56)	
	<65 Years (N=1,238)		≥65 Years (N=301)		<65 Years (N=580)		≥65 Years (N=301)									
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Patients given benzodiazepines	100	8.1	33	11.0	13	2.2	6	2.0	8	8.0	4	4.0	14	33.0	0	0
Patients with at least moderate dose and length of treatment	9	0.7[a] 9.0[b]	4	1.3[a] 12.1[b]	0	0	1	0.3[a] 16.7[b]	0	0	0	0	3	7.0[a] 21.4[b]	0	0
Patients meeting *DSM-III* criteria for abuse/dependence	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

[a] Percentage of patients reviewed.
[b] Percentage of patients prescribed benzodiazepines.

were receiving benzodiazepines, the use of benzodiazepines ranged from 2% in the medical primary care clinic to 11% in the geriatric psychiatry clinic. The number of patients who met the criteria for moderate (or greater) use was quite low, from 0% to 1% of all patients, or 0% to 16.7% of those prescribed benzodiazepines (except for the spinal cord injury clinic, where benzodiazepines were used for muscle relaxation). The major finding was that no patient met the criteria for psychoactive substance abuse or the more stringent criteria for dependence.

A similar study in Austria (5), in clinics comparable to the ones we surveyed, found that 1.3% of the patients had benzodiazepine abuse along with other drug abuse (mainly alcohol), and 0.2% had benzodiazepine abuse alone. Our survey did not include the clinic where patients with alcohol abuse were treated. Our finding of no benzodiazepine abusers is comparable to the 0.2% rate found in Austria.

Other studies of benzodiazepine use by outpatients have differed from this study. Two (6, 7) described benzodiazepine use by patients newly admitted to clincs, and one (8) reported on discharged inpatients followed up at a clinic. None of these studies reported the prevalence of benzodiazepine abuse/dependence.

Our study was limited by the absence of any direct evaluation of the patients. It is possible that the treating physicians were unaware of the patients' symptoms of abuse or dependence and did not record them in the charts or tell the researchers who conducted the interviews.

We conclude that physicians treating outpatients in this public hospital are not causing benzodiazepine abuse. Further research should address whether this finding can be replicated in this and other settings.

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Parental Alcoholism as a Risk Factor in Benzodiazepine Abuse: A Pilot Study

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David J. Greenblatt, M.D., and Richard I. Shader, M.D.

Nine of 12 men with a family history of alcoholism but only two of 12 control subjects had euphoric responses to alprazolam. The authors conclude that sons of alcoholics may be at high risk to abuse alprazolam.
(Am J Psychiatry 1989; 146:1333–1335)

Clinical experience and carefully designed studies indicate that alcoholics are at risk for benzodiazepine abuse (1). In a previous study (2) we demonstrated that alcoholics were more likely to become euphoric following a single 1-mg oral dose of alprazolam than nonalcoholic volunteers without a family history of alcoholism. These findings imply a greater potential for abuse of benzodiazepines when used in the clinical treatment of alcoholics compared with nonalcoholics. Because plasma levels of alprazolam in the two groups were similar, a pharmacokinetic mechanism could not explain the difference in mood effects.

That study raised the possibility that other groups could be at high risk for benzodiazepine abuse. In the present investigation, we studied nonalcoholic adult sons of alcoholics, who are known to be at high risk for alcoholism (3, 4), to determine whether they also had euphoric responses to alprazolam. We used a single dose of alprazolam or buspirone followed by assessment of pleasurable mood effects. The predictive model of abuse liability was the Addiction Research Center Inventory—MBG Scale, a widely used and well-validated paradigm (5–7). With respect to the validity of this instrument for assessing the potential for benzodiazepine abuse, Griffiths et al. (6) found a consistent eightfold difference in potency between oxazepam and diazepam whether measured by changes in the Addiction Research Center Inventory—MBG Scale, number of tablets consumed in a free-choice paradigm, subjective liking scale scores, or estimated street monetary value.

METHOD

Fifteen sons of alcoholics were recruited through newspaper advertisements. All signed informed consent forms and were given physical examinations, psychiatric interviews that included data on family history as well as alcohol and drug intake, measures of blood chemistries, and EKG. A diagnosis of parental alcoholism based on *DSM-III-R* criteria was made following an interview with the subject.

Alprazolam, 1 mg, was administered orally after an overnight fast, and blood samples were drawn before its administration and at multiple points during the 48 hours after administration. Euphoria was defined as a 30% increase over baseline in euphoria scale scores (Addiction Research Center Inventory—MBG Scale). Subjects with euphoria were asked to return for another session with "a similar drug." Of the nine subjects eligible for the second part of the study, five agreed to participate. They were given 10 mg of buspirone orally in an identical protocol.

After each blood sample was drawn, 100-mm analogue scales measuring sedation, euphoria (Addiction Research Center Inventory—MBG Scale), and present mood state (5) were administered. Plasma alprazolam concentrations were determined by gas-liquid chromatography with electron capture detection (8).

The terminal log-linear phase of each plasma alprazolam concentration curve was identified, and the slope was determined by linear regression analysis. The slope was used to determine the apparent elimination half-life. The area under the plasma concentration curve from baseline to the final detectable alprazolam concentration was determined by the trapezoidal method. To this calculation was added the residual area extrapolated to infinity, calculated as the final concentration divided by the slope, yielding the total area under the curve. Apparent oral clearance of alprazolam was calculated as the administered dose (1 mg) divided by the area under the curve. The apparent volume of distribution was calculated as the clearance divided by the slope. The rate of alprazolam absorption was evaluated on the basis of the peak plasma alprazolam concentration and the time of peak concentration.

Chi-square analysis was used to compare the num-

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ber of euphoric subjects in the group of sons of alcoholics with the number of euphoric subjects in a group of control subjects who had participated in an identical protocol run in the laboratory 6 months before the present study. Euphoria scores after buspirone or alprazolam as well as pharmacokinetic measures were compared by using Student's t test; $p \leq 0.05$ was considered significant.

RESULTS

Three subjects were not included in the analysis because they met *DSM-III-R* criteria for alcohol dependence themselves. All three of these subjects had euphoric responses to alprazolam. The mean±SD age for the remaining 12 subjects who were sons of alcoholics was 35±12.5 years, and their mean alcohol consumption was 0.50±1.00 drinks over the previous 7 days, 1.88±3.36 drinks per week over the past month, and 3.22±4.92 drinks per week over the past 6 months. The control subjects were 12 men with a mean age of 39.3±10.7 years without a history of alcoholism in their first-degree relatives. The mean alcohol consumption in the control group was 0.51±0.86 drinks over the previous 7 days, 0.50±0.49 drinks per week over the past month, and 0.59±0.51 drinks per week over the past 6 months. These values did not differ significantly between groups ($p=0.99$ for 7 days; $p=0.13$ for 1 month; $p=0.08$ for 6 months). There was no drug use (including benzodiazepines) during the year before the study in either group. Nine experimental subjects had fathers who met *DSM-III-R* criteria for alcohol dependence, two had both a father and mother who met these criteria, and one had only a mother who met these criteria, but his father had left the family when the subject was young and data were unavailable to make a diagnosis.

Nine of the 12 sons of alcoholics had euphoric responses to alprazolam, compared with two of the 12 control subjects without a family history of alcoholism ($\chi^2=6.04$, df=1, $p=0.01$).

The euphoria scores of the nine sons of alcoholics who became euphoric after alprazolam administration increased a mean of 53.7%±30.0% over baseline; the scores of the five sons of alcoholics who received buspirone increased 15.8%±5.4% over baseline ($p<0.006$). The baseline euphoria scale scores before administration of alprazolam and buspirone did not differ. Euphoria scale scores during the ascending limb of the plasma concentration curve were significantly correlated with plasma alprazolam levels ($r=0.865$, df=53, $p=0.05$) in sons of alcoholics. None of the calculated pharmacokinetic measures was significantly different from measures obtained in a previous similar study (2), with our normal control subjects (see table 1), or in patients with panic disorder (9).

TABLE 1. Pharmacokinetic Measures Following a 1.0-mg Oral Dose of Alprazolam in Sons of Alcoholics and Normal Control Subjects[a]

	Sons of Alcoholics (N=12)		Control Subjects (N=12)	
Measure	Mean	SD	Mean	SD
Age (years)	35.0	12.5	39.3	10.7
Weight (kg)	77.2	11.8	80.5	10.1
Peak plasma concentration (ng/ml)	23.0	5.9	18.4	5.2
Time of peak (hours after administration)	1.02	0.38	1.06	0.85
Elimination half-life (hours after administration)	13.4	5.9	11.7	3.5
Clearance (ml/min per kg)	0.80	0.31	1.06	0.24
Volume of distribution (liter/kg)	1.02	0.38	1.02	0.21

[a] All comparisons were nonsignificant according to Student's t tests.

DISCUSSION

We found that nine of 12 adult sons of alcoholics but only two of 12 control subjects had an increase in euphoria scale scores after a single dose of alprazolam. This suggests that sons of alcoholics may be at higher risk to abuse benzodiazepines than individuals without a family history of alcoholism. The clinical pharmacokinetic measures of the sons of alcoholics were similar to those of control subjects who did not have euphoric responses to alprazolam, indicating that plasma level differences did not account for the different subjective effects. We also found that five of the nine subjects who responded to alprazolam with euphoria did not have a significant increase in euphoria scale scores after buspirone administration.

These findings, although preliminary, have clinical and heuristic importance. From a practical standpoint, caution should be exercised when prescribing benzodiazepines not only to alcoholics (1) but also to men with a family history of alcoholism. In these patients, buspirone may have less potential for abuse.

From a theoretical perspective, a single-dose alprazolam challenge could be studied as a possible marker of susceptibility to alcoholism. We know that the benzodiazepine receptor is linked to γ-aminobutyric acid (GABA) and that the effects of ethanol itself may be partially mediated by GABA and blocked by benzodiazepine antagonists (10). Unfortunately, the current study cannot answer whether the euphoric response to alprazolam can be used to identify subjects at high risk for alcoholism. The mean age of this sample was 35, so that many of the men had passed the period of highest risk for developing alcoholism. Furthermore, most were social drinkers, so it is conceivable that exposure to ethanol may have altered their response to alprazolam. Even so, this would be an important finding, because moderate ethanol consumption did not affect the response to alprazolam in control subjects without a personal or family history of alcoholism.

Although these findings are of potential clinical importance, the preliminary nature of this study should lead to cautious interpretation of the results. As a pilot study, the design was open for the alprazolam administration, was single-blind for buspirone, and did not use a placebo control. It is possible that the initial euphoric effects of alprazolam were due to expectations on the part of the subjects. Although possible, this is unlikely, given that the euphoria scale scores do not show meaningful changes in response to placebo (5). Furthermore, euphoria scores were significantly correlated with plasma alprazolam levels ($r=0.865$).

It is also possible that an order effect was present. Alprazolam was always administered first, and it is conceivable that the initial experience of being a research subject, not the alprazolam, was euphorogenic. This is improbable because alprazolam and diazepam, despite order of administration, consistently produce euphoria in alcoholics whereas placebo does not (5; unpublished data of Ciraulo et al.).

Finally, although any comparison with control subjects from an earlier study cannot assume that the groups are adequately matched, data on the control group were gathered only 6 months before this study was conducted and in the same laboratory under nearly identical circumstances. The control subjects were also comparable to the experimental subjects in age, sex, and alcohol consumption.

CONCLUSIONS

Despite their preliminary nature, our findings suggest that clinicians should carefully question patients about a family history of alcoholism before prescribing alprazolam or other benzodiazepines. Such patients may require closer monitoring for signs of abuse. From a research standpoint, the alprazolam challenge test merits study as a marker of high risk for future alcoholism.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

PERSONALITY DISORDERS

Effective Psychotherapy With Borderline Patients: Case Studies, *by Robert J. Waldinger, M.D., and John G. Gunderson, M.D. New York, Macmillan, 227 pp., $25.00 (reprinted 1989 by the American Psychiatric Press, Washington, D.C.).*

The concept of a distinct type of character pathology distinguished by an almost pathognomonic response to either intensive psychoanalytic psychotherapy or an intimate interpersonal relationship of a frustrating nature practically forced itself into the consciousness of U.S. psychiatrists. The disorder that ultimately, but not without considerable confusion, came to be designated borderline personality has been the subject of extensive exploration, particularly by clinicians who felt that they could discern a definite dynamic understanding as adequately explanatory of the behavioral manifestations of the borderline personality. From the outset, the recognition of this disorder flowed from the reflections and outpourings of clinicians who, despite differences in theoretical orientation, could share the sense of frustration and fatigue that was typical of the regressive transference manifestations seen when these patients became engaged in an unstructured, exploratory type of psychotherapy. The major contributions on the borderline personality came from psychoanalysts working with these patients in analytic psychotherapy, often on inpatient units, before the term and concept were adopted in *DSM-III.* Thus, rather remarkably, a psychodynamically explored disorder entered the psychiatric nomenclature on the basis of dynamic formulations that were then integrated with more typical observable character traits.

As the title of this short but important book indicates, it contains case studies of the psychotherapy of borderline patients. Drs. Waldinger and Gunderson are aware that full-length presentations of the psychotherapy of such patients are rare and have often been done in the service of illustrating the theoretical position of a particular clinician who was developing a mode of understanding the borderline patient. The advantage of selecting five cases from clinicians who all ascribe to a dynamic approach to treatment but not to any one theory of borderline pathology is immediately apparent. When you add to this the reflections on what has transpired in these therapies provided by Drs. Waldinger and Gunderson, who discuss each of the cases as well as comment on the nature of change for the entire group of cases, it is clear what an important sourcebook this volume can be. Its potential for helping clinicians, particularly those in training, should be immediately apparent. There are few training programs in the country where residents in psychiatry are not expected to deal with these most difficult patients in intensive psychotherapy. Here is a book that will help them see other clinicians struggling to establish an effective psychotherapeutic endeavor and succeeding after a long and discouraging preamble to a workable psychotherapy.

When reviewing these five cases I was struck by the impression that the patients, particularly in the early parts of the treatment, were excessively in control of the therapist. This seemed to evolve from some aspect of each therapist's dedication to the continuance of the therapy. Drs. Waldinger and Gunderson comment that as therapists get more experienced they set firmer limits sooner in the treatment and that this, in their experience, often leads to a breaking off of the treatment. There is plenty of room for doubt as to what is going on in these therapeutic encounters, particularly since the prolonged turbulent phase seems to register so strongly and be so costly for the patient.

Although Drs. Waldinger and Gunderson are eclectic in their choice of what they call the two predominating theories of borderline pathology and its treatment, they nonetheless are dedicated to the idea that the regressive transference phenomena, whatever these consist of and require of the treatment and the patient, are a necessary component of effecting substantial and autonomy-producing characterological change. They fail to acknowledge techniques of working intensively with borderline patients at any level of frequency while maintaining control of the disruptive components of the transference. Borderline patients who have been locked in long cycles of threatened suicidality, self-destructive acting out, repeated hospitalizations, and rages at the therapist frequently report in a successful and less stormy treatment that they haven't the slightest insight into what was involved during those terrible times in their previous therapy.

I would suggest that although the psychotherapies described in these cases provide beautiful examples of uncontrolled disruptive transference regressions in borderline patients, the psychotherapeutic interventions described do little to meet the promise of effective psychotherapy specified by this book's title. Whichever theory of borderline pathology the individual therapists ascribed to, they all seemed to be trapped in the treatments that they were conducting. If the borderline patients described in these case studies seem like parodies of psychotherapy patients, then the therapists seem to be the proper templates for these patients' inappropriateness for psychotherapy. In each of these cases the therapist's stance and interventions clearly could be seen to perpetuate the cycle of exaggerated regressive transference demands. The patterns of disruptive behavior, such as wrist cutting, burning with cigarettes, and minor overdoses, were all treated as seriously endangering the patient. Attempts were made to control the patient's acting out, which in turn resulted in the special power and appeal of these particular forms of "self-destruction." In this regard, this book substantiates my impression that overt borderline pathological behavior is always the product of a dyadic relationship between a borderline patient and a significant other. When a psychotherapist is dedicated both to the patient and to the idea that the regressive transference is essential to a psychodynamic therapy aiming at change in personality structure, the result will undoubtedly include stormy periods of massive regression with a focus on and within the transference relationship. Although Drs. Waldinger and Gunderson show that dedicated involvement of the therapist can overcome the patient's destructiveness, lack of motivation for progress, and involvement in outwitting and fighting with the therapist, they fail to prove that the regressive phase is inevitable and necessary for the therapeutic gains that they demonstrate. They certainly fail to question the possibility of achieving change by establishing a therapeutic alliance as a precondition for increased intensity and frequency of the therapy.

In my opinion, there is a paradox in the authors' conclusion that these borderline patients could have been well treated with good results by therapists with differing theoretical approaches as long as they were enduring, caring, and limit setting in their approach. The therapist who ignores any patient's lack of motivation to change is essentially failing in empathic understanding. In this regard, this book fails to grasp Kohut's use of empathy as restricted to an information-gathering technique. The authors view an empathic failure as a lack of nurturing or sympathy rather than a failure to understand what the patient or his or her behavior is about. Kohut felt that borderline pathology was beyond the limits of his empathy because he could not find a cohesive self in the patient. Had he had the opportunity to treat more borderline patients or been required by necessity to see such patients, I believe that he would have found his empathic attunement capable of reading the intense destructive and uncaring lack of connectedness that the borderline patient brings to psychoanalytic psychotherapy. The effort that Drs. Waldinger and Gunderson make to see the violent, uncooperative acting out of these patients as defensive represents, in my view, an unempathic denial of these patients' basic character disorder. Reaction formation and wishful thinking seem to be even more apparent in attempts to view disruptive responses to the therapist as efforts to recapitulate and/or create a tolerable relationship.

Effective psychotherapy with borderline patients, as promised by the title of this book, may require a therapeutic stance considerably at variance with the heroic treatments presented in these five case studies. The therapists all shared a determination to keep these treatments going at almost any price; they all shared a view that the patient's personal wildness and overt contempt for the process of psychotherapy had to be tolerated. In this regard they were, in my opinion, mistaken and unwittingly contributing to iatrogenic aspects of the disorder they proposed to treat. Although one could admire their dedication to the task of psychotherapy, one should also question the role of their denial in proceeding in the fashion that is described in these reports. All of the therapists tried to set limits with regard to behavior, but there is no evidence that any willingness to set limits on their own use of and belief in transference regression as essential and inevitable in such patients was exercised.

This book, then, despite the admirable effort by the authors to present complete cases of treated borderline patients, fails to present a convincing picture of the effective intensive treatment that is potentially available to the borderline patient. Residents in training as well as those associated with many residency training programs, however, will find an all too familiar picture of borderline patients in regressive states related to a motivated psychotherapist. The fact that all five patients managed to survive these regressive states and develop as individuals with seemingly normal capacities to relate to a therapist is encouraging, but, without the presence of comparative cases of patients treated without such regression, it will remain difficult not to be misled by the "success" of these cases. Furthermore, despite the authors' acknowledgment of these patients as having higher-level borderline personality, the presentation undoubtedly will encourage too many young psychotherapists to embark down a regressive pathway, which more often than not represents a road of no return rather than the temporary, if prolonged, voyages described here. I, for one, would advocate less therapeutic optimism with borderline patients and more adherence to principles of treatment that require absence of a destructive attitude toward the therapy on the patient's part. Good results are of course important, but this book reminds us that we must ask at what price they are achieved and if there is a more effective, less destructive mode of achieving the same results.

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Personality Disorders: Diagnosis, Management, and Course, *edited by Peter Tyrer, M.D. Littleton, Mass., PSG Publishing Co., 1988, 200 pp., $75.00.*

This book is a valuable reference work for clinicians and researchers interested in clinically relevant personality pathology. Although it appears that a major part of the motivation behind writing this work was to introduce readers to the Personality Assessment Schedule and related work, in laying the groundwork to do so Dr. Tyrer has provided an excellent review of much of the empirical literature on clinically relevant personality measurement. By clinically relevant I mean that he approaches the problem as a medical clinician rather than as a personality theorist. The book, in fact, does not spend a great deal of time on theoretical issues, although they are discussed.

The book is deceptively brief. Although different chapters are written by different authors, they all tend to be pithy and are not given to excessive elaboration of ideas. They are not, however, without occasional dry wit. On page 61, when referring to personality measures tied to *DSM-III,* Dr. Tyrer writes, "Unfortunately, those scales that are wedded to *DSM* have to follow their wayward bride wherever she chooses to take them, and at present she shows no signs of settling down."

The chapters include, among other topics, the development of the concept of abnormal personality, classification of personality disorder, reliability and validity of personality assessment, epidemiology of personality disorder, personality disorders and other mental illnesses, management of personality disorder, and outcome of personality disorder. Most of these chapters are strong, although I agree with Dr. Frances's statement in the foreword that Dr. Tyrer may be a bit pessimistic about the future of treatment for these disorders.

For personality researchers, this book represents a special opportunity. Included in it are everything needed to use the Personality Assessment Schedule. This includes instructions, a copy of the schedule and a scoring sheet, scoring instructions, and even preliminary conversion formulas to create *DSM-III* axis II diagnoses. It appears that Dr. Tyrer is generously offering the use of his instrument to interested parties.

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The Psychopathic Mind: Origins, Dynamics, and Treatment, *by J. Reid Meloy, Ph.D. Northvale, N.J., Jason Aronson, 1988, 460 pp., $40.00.*

This substantial volume is by a psychologist who is Chief of Forensic Mental Health Services for San Diego County, Calif., and an adjunct professor at the San Diego School of Law. Part one, Origins, begins with an introductory chapter. The author prefers the term "psychopathy" to "sociopathy" or "antisocial personality," which have all been used to designate the problem.

Dr. Meloy considers psychopathic personality organization to be a variant of narcissistic personality organization distinguished by seven characteristics that include aggressive drive derivatives, sadistic and cruel behavior, and the absence of a desire to morally justify one's behavior. He reviews the evidence for genetic elements in criminal behavior from twin studies and adoption studies. He explores the evidence regarding the role of neurotransmitters, hormones, and autonomic activity. Psychopathic individuals tend to be autonomically hyporeactive.

Dr. Meloy emphasizes the common history of child abuse in the background of psychopaths. He explains the psychopathic process as a virtual failure of internalization, with a lack of "soft" sensory experiences and a predominance of "hard" experiences. His explanations are psychoanalytic (he is a practicing psychoanalyst). Whether one feels enlightened or not by his psychoanalytic terms, the association of lack of nurturing with the development or failure of development of the psychopathic individual is generally recognized. There is a failure of attachment to or identification with a parent figure.

In discussing mammalian evolution, Dr. Meloy states that in reptiles, the limbic structures of the brain are generally absent. With this absence is an absence of such mammalian behavior as parental responses toward offspring, food hoarding, and social behavior. In important regards the psychopath behaves at a reptilian stage of development.

Dr. Meloy differentiates affective aggression, which is reactive to external causes and events and involves autonomic hyperreactivity, from predatory aggression. In animals, predatory aggression is usually in the interest of food gathering. In predatory aggression, autonomic arousal is minimal or absent. Predatory violence is not reactive but is typically planned. If strong emotion is aroused, it may be exhilaration with successful aggression, and this may lead the psychopathic killer to find ritual ways to taunt the authorities in the arrangement of the victim's body. The author also presents cases in which elements of psychosis combine with elements of psychopathic process: "The psychotic state will be aggressively expressed and malevolently used to perpetuate the sadomasochism of the grandiose self-structure" (p. 257).

Dr. Meloy rejects the idea that the psychopath is untreatable, but he recognizes the paradox that confronts the therapist: the subject should be believed, but the prediction is that the subject will try to deceive. He emphasizes that it is important to recognize psychopathy as a matter of degree rather than as an all-or-none phenomenon. Dr. Meloy does grant that there is some psychopathy so severe as to make psychotherapy inadvisable. The degree of psychopathy determines the treatment needs, ranging from weekly sessions with the mild case to secure and highly structured and controlled inpatient care for the severely psychopathic. The treatability of the psychopath depends on his or her capacity to form attachments and on the degree of superego pathology—the degree to which the subject lacks conscience.

The book is enlivened by many vignettes extracted from Dr. Meloy's own experiences and from publications by professionals who have studied such classical cases as the Boston Strangler, Son of Sam, and Ted Bundy. This is not an easy book to digest, but it contains a great deal of information and can be recommended to those with a serious interest in the problems of psychopathy and the psychopath.

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BASIC BIOLOGICAL FUNCTIONS

Bulimia: Psychoanalytic Treatment and Theory, *edited by Harvey J. Schwartz, M.D. Madison, Conn., International Universities Press, 1988, 549 pp., $55.00.*

When I read the introduction to this book, memories of my first medical school psychiatry class came rushing back. A prominent psychoanalyst presented the first lecture. She described the use of circumcision in the treatment of a teenage woman with an eating disorder. Although I still do not understand the justification for this brutal treatment, psychoanalytic theory has helped us to understand the genesis of eating disorders. Dr. Schwartz, editor of this volume, provides a meaty overview of psychodynamic concepts in his brief introduction, which serves as an excellent lead-in to the remaining 16 chapters.

I was happily surprised that the chapters are uniformly well written. The contributors, well-known in their respective fields, help the reader to understand bulimia: its development, self-destructive behavior, gender and age specificity, genital components, and social interactions in the home and at work. The authors also help us understand the rationale for both individual and family therapy of the bulimic patient. Through the use of instructive case material, the chapters take a clinically oriented approach to problem solving. This approach helps to enlighten rather than obscure the use of psychoanalysis in the treatment of these difficult patients.

Dr. Schwartz also provides two additional chapters. In a chapter on psychodynamic perspectives on bulimia, he presents the development of object relations and demonstrates the importance of unresolved oedipal conflicts as the foundation of the defensive structures of "displacement, regression and narcissistic condensation" involved in the clinical picture of bulimia. These problems are not often addressed because most clinicians and patients wish to skim the surface of the problem by treating only the symptoms and not the cause.

Dr. Schwartz builds further on the oedipal conflict in his second chapter, "The Mouth-Vagina Equation." He presents extensive clinical material based on his 3-year treatment of a difficult patient. He concludes that narcissistic injuries that develop during the phallic phase result from the absence of external, visible, and touchable genitals and that the young woman begins to feel worthless and unloved. Injury at this particular stage of development leads to regression and the displacement of castrating fantasies to the eating disorder and the often associated kleptomania.

Dr. Schwartz stresses the importance of social forces, child-rearing practices, and parents' acknowledgment of their own sexual identities in the psychosexual development of the child. These factors must be addressed for the development of a comprehensive treatment plan.

Several chapters emphasize a more integrated approach to treatment by combining psychotherapy, behavior modification, and, if the need arises, medication. Dr. Remi Gonzalez addresses the role of individual psychodynamic psychotherapy in the adolescent patient. He describes the typical patient as "a single, white female in her early twenties who is well educated and of average weight, . . . [is] frequently impulsive [and] moody, complains of both anxiety and depression, . . . [is] confused about [her] sex-role identity, and [is] severely preoccupied with food, weight and thinness."

Such descriptions should raise questions in the mind of the reader about the comorbidity of bulimia, depression, substance abuse, and personality disorder, which have recently been acknowledged by many investigators. Unfortunately, this text does not emphasize the interplay of eating disorders and other psychiatric syndromes.

Dr. Kent Ravenscroft emphasizes family therapy, since the bulimic patient's behavior may be the manifestation of familial and marital conflict. This conflict is difficult to deal with, since the bulimic patient may view the analyst as an agent for parental subjugation. Dr. Ravenscroft's approach is novel, for, as he points out, there has been little research and "no references from the psychoanalytic family therapy school on bulimia."

Although Dr. Schwartz considers the biology of the mind an esoteric pursuit in the treatment of bulimia, Dr. Martin Caesar, in "Integrated Approach to the Understanding and Treatment of Bulimia," stresses that a complete diagnostic workup and consultation with an internist is needed. He also points out interesting work being done on the overlap of bulimia with affective disorders and the importance of nutrition.

The book ends with a clinical vignette of a patient whose eating disturbances were associated with kleptomania directed toward food and toward useless objects. The patient was acquitted when brought to trial for thefts but died when she was hit by a car as she was greedily swallowing a sausage she had just begged from someone.

The cause of bulimia is unknown, but much speculation exists. From a psychodynamic perspective, this book presents an excellent review of the historical and theoretical underpinnings of bulimia, as shown by the extensive list of references, some dating back to the close of the nineteenth century. Few references are made, however, to the extensive biological and behavioral research undertaken in this area (1–3). Because the book is, therefore, not comprehensive, I cannot recommend it to data-oriented psychiatrists or generalists. I can recommend this book, however, for those with a strong interest in the dynamically oriented treatment of eating disorders.

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Human Sleep: Research and Clinical Care, *by Wallace B. Mendelson, M.D. New York, Plenum, 1987, 436 pp., $49.50.*

Dr. Mendelson's work is one of several books dealing with basic sleep research and sleep disorders medicine to have appeared in the last 2 years. *Human Sleep* is the only one written by a single author, which leads to many strengths and a few weaknesses. Certainly the author is superbly qualified to write such a volume, having been directly involved in many of the research and clinical areas discussed.

Dr. Mendelson indicates in the preface that his goal is "to describe the physiology and pharmacology of sleep . . . and to relate them to clinical sleep disorders." He further states that what he offers is a snapshot rather than an encyclopedia of the field. The reader will do well to heed these caveats: *Human Sleep* does not offer a comprehensive textbook on sleep and its disorders but a personalized and at times idiosyncratic view of research and clinical care. The author might have specified his desired audience more clearly, since some sections appear to be written for newcomers and others may be beyond the scope of many seasoned practitioners and researchers.

The author's choice and organization of topics reflect his own interests in the field. Thus, topics not included are as telling as the emphasis placed on topics that are included. For example, there is one consolidated paragraph dedicated to general physiology during sleep but 25 pages devoted to the regulation and secretion of growth hormone. An entire chapter describes the benzodiazepine receptor, but there is no consolidated section on the anatomy of sleep. Another entire chapter reviews the effects of alcohol on sleep, but no chapter on parasomnias is included.

The book is divided into two sections, the first dealing with basic physiology and pharmacology and the second discussing common pathologies of sleep. There is no general introduction to the first section, but there is for the second; such an introduction would have helped to tie together the various topics discussed. It is unclear why the chapter entitled "Pharmacologic Treatment of Insomnia" is included in the first rather than the second section of the book.

The first section includes "An Introduction to Sleep Studies," "Pharmacology and Neurotransmitters in Sleep," "Pharmacologic Treatment of Insomnia," "The Benzodiazepine Receptor in Sleep," and "Neuroendocrinology and Sleep." The scholarship in this section is uniformly excellent, the references complete, and the writing crisp and easy to follow. Several chapters present more detail than the general reader will desire; the entire chapter on benzodiazepine receptors, in fact, will likely be of interest primarily to those involved in receptor pharmacology. However, the author offers brief, general summaries at the end of his chapters to highlight major points. Although these chapters present excellent reviews, they are most interesting when they go beyond the "facts" to discuss theoretical aspects and models of physiological systems. Much of basic sleep research is riddled with conflicting results. Dr. Mendelson should, perhaps, have placed greater emphasis on synthesizing the findings he presents and offering possible resolutions to controversies. At times, too, the chapters in this section could have used stricter organization. For example, the introductory chapter presents many different topics that might have been organized into larger sections to help the reader, and the neuroendocrinology chapter might have more thoroughly explicated how endocrine and sleep regulation are tied to each other.

The second section of the book presents chapters on common sleep pathologies, including sleep apnea, narcolepsy, alcohol dependence, affective disorders, circadian rhythm disorders, nocturnal myoclonus, and chronic insomnia. Once again, these chapters are all very thorough and readable, providing an excellent introduction for the newcomer and an excellent review for those already involved in sleep disorders medicine. The clinical material is well organized and up-to-date. As in the first section, Dr. Mendelson is at his best when discussing theoretical models and implications; the sections on affective disorders and circadian rhythms are particularly enlightening in this regard.

Although *Human Sleep* covers the major sleep disorders, some topics are not addressed at all. Examples include parasomnias, childhood sleep disorders, and medical/surgical conditions affected by sleep. There is certainly no obligation to discuss every known sleep disorder, but a naive reader might erroneously assume that the pathologies discussed by Dr. Mendelson are the only important ones currently recognized. The book does not present any complete outline of a sleep disorders nosology, in a unified way, such as the classification developed by the Association of Sleep Disorders Centers. Doing so might have provided a more balanced approach, even if all disorders were not presented or discussed in detail.

Overall, *Human Sleep* is praiseworthy for its detailed scholarship, complete references, and discussion of both research and theoretical findings. On the other hand, targeting a more specific audience and offering more synthesis of the findings it presents would have further enhanced its value. The introductory and clinical chapters, in particular, will be very helpful to the new student of human sleep and its disorders. Some readers may take issue with the topics selected for inclusion and exclusion, just as they may find any snapshot more or less to their taste.

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Medical Aspects of Anorexia Nervosa, *by S. Bhanji and D. Mattingly. Littleton, Mass., PSG Publishing Co., 1988, 180 pp., $45.00.*

Anorexia nervosa is a potentially fatal eating disorder that primarily affects females in adolescence or young adulthood. It is known to be associated with numerous potential medical problems involving nearly all organ systems. Questions remain as to which medical problems of anorexic patients are part of the primary illness and which are complications.

The authors of this book state these objectives in their preface: "To focus on those medical aspects of anorexia nervosa which may affect both management and prognosis, and to discuss its treatment." The book accomplishes these objectives in a pleasantly brief, succinct, and readable format. For those desiring more detailed information, each chapter is followed by an extensive list of references.

After briefly reviewing the history of anorexia nervosa, its clinical characteristics, and its hypothesized etiologies, the authors present the medical "aspects" of anorexia, including nearly all possible associated physical and laboratory findings. Some of these findings, such as endocrinological abnormalities indicating probable hypothalamic dysfunction, may be additional manifestations of the same basic disturbance causing the anorexic syndrome. Other findings, such as hypokalemia in laxative abusers, are clearly late complications.

The book's format allows one chapter for discussion of each organ system. For example, the chapter entitled "The Cardiovascular System" contains concise subdivisions addressing peripheral circulatory abnormalities, heart size, ECG findings, myocardial efficiency, occurrence of mitral valve prolapse, ipecac cardiotoxicity, and congestive heart failure as a complication of refeeding. Complications involving the respiratory, nervous, gastrointestinal, and hematologic systems are presented in turn, as well as thorough discussions of endocrinological and metabolic abnormalities.

Therapeutic approaches to anorexia nervosa, including psychotherapy, pharmacotherapy, and behavior modification, are also reviewed. The authors acknowledge that the discussion of psychotherapeutic and behavioral techniques is brief and superficial, and these topics are certainly better addressed by other sources. However, studies of pharmacotherapy for anorexia, including the use of insulin, antipsychotics, and antidepressants, among others, are well presented in the extensively referenced chapter on medical management. The authors go on to present their own management regimen, consisting of hospitalization on a medical ward, bed rest, insulin, and antipsychotic medication.

Two final chapters review studies of prognosis and treatment outcome in anorexia nervosa and present evidence for viewing bulimia nervosa as a separate diagnostic entity.

This work presents a concise, readable, and easily accessed review of a large body of literature on medical aspects of anorexia nervosa. For that reason, it will find its place as a useful quick reference for the clinician who treats anorexic patients, especially patients on inpatient units, who frequently have or develop medical complications.

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Diagnostic Issues in Anorexia Nervosa and Bulimia Nervosa, *edited by David M. Garner, M.D., and Paul E. Garfinkel, M.D. New York, Brunner/Mazel, 1988, 228 pp., $25.00.*

It is appropriate that within the first few pages of this monograph Gerald Russell reviews the stages in the growth of knowledge of a disease; this deftly sets the tone for the balance of the book. Those stages of knowledge, attributed to Scadding (1967), are 1) the descriptive diagnosis, 2) the pathological diagnosis, and 3) the etiological diagnosis. The book, then, is a collection of chapters by some of the more published authors in the field of eating disorders. The chapters explore important diagnostic dilemmas in anorexia and bulimia. One is led to the conclusion that our present level of knowledge regarding these two disorders is precariously perched at stage one, with stage two just visible on the horizon.

The issues addressed are of importance to all clinicians but may be especially pertinent to the consultation-liaison psychiatrist because, as Anderson points out, "Of our consultations from the general medical or surgical inpatient services for evaluation of possible eating disorders, 75% have led to other diagnoses." He further states that "complicated or chronic illnesses that have no clear findings on standard testing lead physicians to consider a diagnosis of eating disorder when weight loss or vomiting are involved." In other words, it is important for the consulting psychiatrist to recognize when a primary eating disorder is not present, so that other appropriate diagnostic workup is not delayed.

Bulimia nervosa is the newer of the two diagnoses and as such has probably undergone more diagnostic scrutiny in recent years. The entirety of chapter two is devoted to discussing the differences in diagnostic criteria between *DSM-III* and *DSM-III-R*. It is pointed out that, in the course of arriving at the new criteria, "not all committee members agreed on every point." The resulting revised criteria are narrower than those of *DSM-III*, and the argument is made that "since our knowledge of bulimia nervosa is still in a relatively early stage, it seems better to err on the side of narrowness than on the side of breadth." Gerald Russell, in chapter one, points out the limitations of "simply ascertaining whether a patient fulfills the diagnostic criteria," arguing additionally for inquiry into psychopathology, severity of eating behavior, premorbid personality, and presence or absence of affective symptoms in bulimic patients. It appears that several of the issues that he raises have at least partially been addressed in the *DSM-III-R* criteria changes.

One of those major changes in *DSM-III-R* is the addition of a criterion necessitating that the bulimic patient display "persistent overconcern with body shape and weight." This is a feature that has long been associated with anorexia nervosa. In chapter three, Fairburn and Garner stress the diagnostic importance of this characteristic psychopathology and discuss several of the research instruments currently being used to assess this variable. The same authors discuss the relationship between anorexia nervosa and bulimia nervosa, concluding that there is a great deal of overlap between the two according to current diagnostic strategies. Their review of the literature notes that the presence of bulimic behavior carries with it certain prognostic implications, irrespective of the patient's present or past weight. They summarize by proposing that the diagnosis of bulimia nervosa should "trump" that of anorexia nervosa and that the latter be reserved exclusively for the restricting anorexic patient.

A common diagnostic dilemma involves the dysphoric individual with eating abnormalities; is this an eating disorder, an affective disorder, or both concurrently? There is a large body of literature on this issue, and Strober and Katz review this literature in their chapter. Unfortunately, the answer is no more clear at the end of the chapter than it is at the beginning. The hypothesis that eating disorders represent simple variants of affective disorders is rejected. Affective disorders, particularly depression, share many common risk factors with the eating disorders, and true comorbidity certainly exists. Clear subgroups of patients in whom depression is secondary to the eating disorder (or vice versa) have not yet been defined, and the reader is left with a call for more research in this important area.

The book is rounded out by a chapter addressing personality characteristics in patients with eating disorders, which concludes that "the domain of personality and eating disorders remains largely unknown," and a chapter on eating disorders in males, which reminds the reader that male sex is not an exclusion criterion for the diagnosis of either anorexia or bulimia.

Diagnostic Issues in Anorexia Nervosa and Bulimia Nervosa is the second book in the Brunner/Mazel Eating Disorders Monograph Series; however, it could easily stand alone. It provides a concise, easy-to-read review of the literature on the issues in the diagnosis of eating disorders that often face clinicians. It does not pretend to be able to answer questions on which "the jury is still out." The discussions of the theory underlying the diagnostic criteria would be worthwhile reading for any clinician. Consultants who see patients with weight or eating abnormalities on medical or surgical services in whom the diagnosis of a primary eating disorder is being considered may find the information in this book particularly useful.

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PSYCHOTHERAPY

Confessions in Psychotherapy, *by Sharon Hymer, Ph.D. New York, Gardner Press, 1988, 297 pp., $24.95.*

This unique book covers the subject of confessions from many points of view. Although the logical progression of the chapters is predictable and traditional, Dr. Hymer's presentation poses new and different questions that go beyond the focus of her volume. Since she specifically deals with confessions in psychotherapy, her chapters center on the clinical situation. Her opening chapter addresses such questions as the difference among confessions, other therapeutic interchanges, and religious admissions of guilt as well as the connection between confessions and self and object relations development. An interesting clinical example—the first of many interspersed throughout the book—illustrates the theoretical constructs she discusses. Dr. Hymer then discusses patients' motives for confessing, such as guilt or a wish for acceptance. In discussing the therapeutic functions of confession Dr. Hymer deals with such issues as trust and intimacy. Here the references to catharsis could have been elaborated. Skipping theoretical discussions of the work of Erikson, Mahler, and Kohut, the author introduces her idea of the confessional process. She identifies risk, relief (catharsis?), redemption, and renewal as stages in this sequence.

The next theme she develops deals with childhood, adolescent, and adult confessions. She also writes about preoedipal and oedipal confessions and how confessions assist in the consolidation of the self. Dr. Hymer addresses the nature of the object in confessions, ethical and legal dilemmas involving confessions, and transference and countertransference dimensions of the confessional process. Whether analysts should or should not confess, how much analysts are or are not aware of in their confessions, and the advantages and disadvantages of the different "confession positions" are also examined.

Dr. Hymer's conclusion that "confessions present a paradox" (p. 265) because they are associated with either religious or forbidden content is also cogent. Her unique position is that confessions can be viewed as contributing to our understanding of the therapeutic situation and are different from other aspects of this clinical experience.

I believe her chapter on betrayal warrants a special emphasis. Her literary references are helpful in illustrating some of her special emphases—e.g., control, victimization, and abandonment. I would add issues of the absence of confidentiality, privacy, and empathy on the part of therapists. Rarely addressed are the ethical dilemmas that result when therapists impose their own value systems, and this includes defenses against their own mishandling of the ethics of confidentiality and, sometimes, suspension of their judgment. One cannot and should not overlook gossip, inuendo, and betrayal, which can be observed in social settings when the therapist suspends therapeutic decorum for personal esteem enhancement. This is damaging to the therapist, the patient, and the profession.

The therapeutic benefits of religion, a topic increasingly studied, are not discussed, nor is the issue of atonement. We read and see more of this in our moral dilemmas concerning wars, holocausts, and other unjust betrayals of basic human rights.

Confessions, memoirs, diaries, correspondence, and autobiographies are very popular these days. Do they result in some therapeutic gains? Do they help individuals and groups rationalize that which they cannot face directly out of fear, shame, guilt, envy, jealousy, self-justification, and reinforcing self-righteousness?

The purpose of therapy is to help patients. There are many kinds of therapies. We can best assist those who come to us by helping them separate myth from reality, allegations from verifiable facts, raw and primitive emotion from careful assessment of actuality, and belief from truth. Dr. Hymer's writings stimulate many questions that not only remain unanswered but hint at others which are not even asked. She has suggested some new vistas that for now are sketchy at best but warrant our serious consideration.

Dr. Hymer's bibliography is very complete. Her writing is clear and appropriately referenced, and her index is adequate. The book might have had tighter organization, and the distinction between psychotherapy and psychoanalysis could have been more sharply defined. However, all in all this is a volume that should be read and discussed further.

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Self and Others: Object Relations Therapy in Practice, *by N. Gregory Hamilton. Northvale, N.J., Jason Aronson, 1988, 330 pp., $30.00.*

Self and Others is a broad overview of current thinking on object relations theory. Generally it is well organized and covers the waterfront of this increasingly popular way of psychoanalytically assessing a patient and deriving technique from its theoretical assumptions. Along with classical conflict theory, ego psychology, and self psychology, object relations theory has helped to change psychoanalysis from the more monolithic body of knowledge it was two decades ago into what many consider an increasingly eclectic field. Dynamically oriented therapists should be familiar with the tenets of object relations theory. My suspicion is that any such therapist, whether he or she be friend or enemy of this system, will find clinically useful ways here to help patients, especially many of the patients who, often by definition, are outside of the conceptual borders of classical psychoanalytic theory.

Not all contemporary psychiatric books have the pleasure of being kept neat and clean by a dust jacket. This book does. Generally, as any rare book dealer would affirm, a dust jacket will raise the worth of a book up to five times. I am not so sure that the jacket of *Self and Others,* perhaps 50 years from now, will help. Not because of form, which is acceptable, but because the content almost makes it seem to belong to another book. In fact, I find that the jacket inadvertently serves as a metaphor for a few of the book's problems.

The main issue is, Who is the target reader of *Self and Others*? After claiming that Dr. Hamilton has succeeded in the task of integrating the "disparate lines of thinking" in modern psychoanalysis (certainly the achievement of a formidable goal), James Grotstein terminates his rather idealized dust cover blurb with these words: "This book best approximates what every psychiatric resident, clinical psychologist, psychiatric social worker, and analytic institute candidate would have wished for. It is an extraordinary handbook of the new developmental psychologies of psychoanalysis."

By placing residents and candidates in with practicing professionals, the blurb becomes confusing. What happened to the psychiatrist who has finished his or her training and to the graduate analyst? Then, in a kind of object relations "split," on the front of the jacket the subtitle proclaims that this is an exposition of *Object Relations Theory in Practice.* I don't think Dr. Hamilton meant the word "practice" only in the sense of trying something out. It certainly implies that the practitioner is involved. So the question arises, Is this a handbook for the beginner or is it a book that the average psychodynamically oriented therapist, "grown up" as well as beginner, could use? I think that the author and the editors were not sure. The book is organized as a kind of handbook, with, for example, the first four chapters entitled "The Object," "The Self," "Self-Object," and "The Ego." Part two is a good summary of Margaret Mahler's separation and individuation developmental line and demonstrates how it is one of the major bodies of knowledge that informs object relations theory. In this respect, for the most part, the book is well organized and complete.

The possibility that this is a book for the rank beginner is reinforced frequently by a talking-down style that could be irritating to the professional. On page 124, when presenting a somewhat complex chart that correlates developmental stage, diagnosis, and level of personality organization, the author introduces the chart with the words, "Here is such a schema." This is typical of Dr. Hamilton's kindergarten style, as opposed to his alternating adult, twentieth-century, discursive "psychoanalyticographic" style, which is good enough for any of the members of the analytic community of readers. How to account for this unfortunate combination of two styles? Did the author and/or editors change horses in the midstream of what Grotstein calls this "object-relations guided tour"? Did some of the author's writing in "grown-up" journals get transcribed without downgraded translation and then lumped with his elementary school, manual style? Let the reader ponder the mystery.

As I have already stated, basically this is a good book. Looked at without my concern about stylistic matters, it presents the historical, theoretical contexts of object relations theory along with its applications. It is chock-full of clinical examples. Most of them are in vignette form, but they are pertinent, well thought out, and most helpful. It is unusual to have so many examples to illustrate an author's points virtually throughout a book. This is where the praxis part is involved, and it seems to be directed to the therapist out there in the community as much as it is to the beginner.

I do think the more experienced reader will miss an updated version of Mahler's autistic phase. Although Dr. Hamilton cites researchers who showed that the very young infant is not without some ability to sense and perceive, he does not even cite the work of Stern, Emde, Sander, or others who showed that wired-in capacities to differentiate and integrate perceptions are present from early on. It is becoming well-known that before her death Mahler really gave up her concept of an autistic phase.

The book has as an appendix a chapter on an object relational applied analysis of folklore, myth, and fairy tale that smacks of the tendency of any new system in psychoanalysis to redo the applied work of the early pioneers in new terms and try to find again the current theory out there in the culture from which it was in part derived. These attempts come out more reductionistic in their tone than I am sure the author intended. On the other hand, his attempt to apply object relations theory to inpatients, large and small groups, psychiatric units, family units, and patients with multiple personality, although brief, are most commendable. So, a somewhat mixed review, but if you want to know what is happening in current object relations theory, read *Self and Others.*

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The Betrayal of the Self: The Fear of Autonomy in Men and Women, *by Arno Gruen; translated from the German by Hildegarde and Hunter Hannum. New York, Grove Press (Random House, distributor), 1988, 149 pp., $16.95.*

The author's thesis is stated in his opening sentences:

> Human development may follow one of two paths, that of *love* or that of *power*. The way of power, which is central in most cultures, leads to a self that mirrors the ideology of domination. This is a fragmented, split self that rejects suffering and helplessness as signs of weakness and emphasizes power and control as means of denying helplessness. The attainment of what passes for success in our world presupposes a self of this nature.

Such a self represents the impairment or loss of autonomy as defined by the author. His definition of autonomy is far broader than the usual one. It implies being in touch with one's feelings and operating from a healthy core capable of protecting oneself from the power plays and manipulative strategies that pass as normal aspects of social intercourse.

Dr. Gruen writes in the tradition of that divergent school of psychoanalysis which concerned itself more with the social than the biological roots of human disorder. Beginning with Adler's concern with power, it was followed by Horney's tempering of Freud's instinctual approach, Sullivan's concern with the interpersonal milieu of the child, and finally and most ambitiously, Fromm's view of behavior as shaped by the contradictions of capitalist society. Gruen's analysis differs in an important respect from that of his predecessors. He not only shares the psychoanalytic and broad political and social perspectives of the others but also brings to the task a thorough grounding in experimental, physiological, and social psychology. A refugee from Nazi Germany in 1936, he had a combined career in the United States as a practicing therapist and a professor of psychology at Rutgers University. (He has been living in Switzerland since 1979.) The statements he makes about the misfiring that goes on between mother and infant, the split that develops between the inner world of the child and its response to the demands imposed on it, and the increasing dependence on external stimuli for a sense of aliveness are all buttressed by experimental data and converging lines of inquiry from ethology to the insights of gifted writers.

Gruen addresses what he sees as a generalized impoverishment in our ability to deal with each other decently and humanely. There is a general malaise abroad arising out of a deadening of the self and manifest by destructiveness on both an individual and a broadly social level. His concern is with the origin of this impairment in the early mother-infant relationship and its further nurturance by the allegiance of those with whom the child comes in contact to a system of external values having no organic connection to inner growth. There results a compulsive dependency on an ever increasing range of stimuli to maintain a precarious sense of aloneness. The end result is entrapment in an addictive mode, lost at one pole in the drug world as social outcasts or at the other as esteemed and successful members of society equally trapped in the pursuit of power.

Gruen's arguments are pursued in depth in his analysis of the role abstraction plays in leading us astray in maintaining disorder, in how male-female stereotypes reinforce patterns of domination and submission, and in how unwittingly the therapeutic endeavor also becomes caught up in it. Reading this book, I found an interesting parallelism between the main points being made by the author and the writings of a much earlier psychoanalyst, now largely forgotten. I refer to Trigant Burrow, who played a role in introducing psychoanalysis to the United States, became president of the American Psychoanalytic Association, and was later alienated from that organization because of his dissident views. Burrow (1) also focused on the early infant-maternal relationship and spoke of the preconscious stage of development, referring to the sense of total unison experienced by the infant with its environment, a stage that then served as a potential template for future relatedness. Burrow's emphasis was also on our failure to preserve this organic sense of connectedness, and, like Gruen, Burrow pointed to the way our capacity for symbolic expression lends itself to misuse and becomes "a poor makeshift for the bond that unites us organically" (1, p. 11). Burrow, too, felt that therapists were unaware of their own role in perpetuating what he referred to as the "social neurosis": "As I see it, the psychoanalytic situation offers a choice between two distinct positions—the one clinical and prescriptive, the other sociological and empirical" (1, p. 45).

In view of the problems facing mankind, the need is even greater today than ever before for the exploration of the relationship between social and personal disorder. Arno Gruen has engaged with this challenge in both a passionate and a scholarly fashion. I hope his voice is heard.

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How Does Treatment Work? On the Modes of Therapeutic Action of Psychoanalytic Psychotherapy, *edited by Arnold Rothstein. Madison, Conn., International Universities Press, 1988, 242 pp., $32.50.*

The question posed in the title of this monograph goes to the heart of psychoanalytic theory. Any answer carries along with it implications about what causes psychopathology. The classical position, that pathology derives from psychic conflict and cure from insight into that conflict, was broadened considerably by Hans Loewald (1) (who has a chapter in this book) and Leo Stone (2) in the early 1960s. They introduced important ideas about experiential factors in the patient-analyst relationship that contribute to cure. In more recent years the self psychologists have argued that such experiential factors form not only one aspect but, indeed, the crucial aspects of the analytic cure. The 16 chapters in this book span a range of views, from the classical to the self psychological.

All of the contributors are psychoanalysts, and all but one, David Werman, focus on psychoanalytic treatment rather than psychotherapy. Thus, the title is something of a misnomer. This is unfortunate, since psychoanalytic psychotherapy (and perhaps psychoanalysis as well) is in need of not only a wider audience but also a wider source of contributors. Nevertheless, this book makes clear that psychoanalysis has come a long way since 1960. One way this is reflected is in the open-minded and tolerant coexistence of conflicting theories. Most of the contributors cannot easily be placed on one side or the other of the experience-versus-insight dichotomy. Most integrate aspects of each side to form theories that differ more in terms of how much and in what ways each perspective is used. Some contributors seem to do away with the distinction entirely. Fred Pine writes that the treatment of every patient involves elements of drive, ego, object relations, and self psychologies. Which of these factors is curative depends on the individual patient. Edgar Levenson states that "it is not an issue of 'insight versus relationship,' but rather the isomorphism, the similarity of form, between the two that defines psychoanalysis."

Others are less ecumenical in their treatments. Paul Ornstein and Arnold Modell present the strongest arguments for the relationship side, and Manuel Furer and Paul Gray do the same for the other. Each shows through case reports how movement in one direction brings with it additional theoretical baggage. Emphasis on insight as the curative factor tends to be associated with less activity by the therapist, a striving toward therapeutic neutrality, and the use of interpretation to bring about insight. Emphasis on the relationship as the curative factor is associated with attempts to produce a corrective emotional experience in the treatment to help the patient resume development that had been arrested. This in turn implies greater activity on the therapist's part, with the focus on empathy rather than interpretation. One should not be overly reductive in defining these dichotomies, however, since many of the authors integrate them in original ways.

The most compelling part of this book comes at the end in the chapters that critique what preceded them. These authors are more successful at what they undertake, although their task is certainly easier. Dale Boesky places himself on the insight side but for different reasons than others. He points out that others show little agreement on what "cure" means or on how to prove that cure has occurred and so are unlikely to agree on how to bring it about. He believes that the only way to begin to come to some agreement is by analysis of detailed case reports. Since such reports must be based on the verbal exchange between patient and therapist, the verbal elements will come to the fore as the curative factors. Donald Spence compares the current state of the art in psychoanalytic treatment with that of the treatment of scurvy before the discovery of vitamin C to highlight how our theories are based on guesses, not facts. He goes on to make some important suggestions on how to acquire a greater factual basis. In conclusion, however, he retreats to his familiar position that it is the shared repetitive themes in the analytic relationship, regardless of their relationship to the facts of the patient's life outside the analytic setting, that contain the curative factors.

How Does Treatment Work? provides an informative survey of current psychoanalytic thought on a question of central importance to the practice of psychotherapy. By excluding nonanalysts from this discussion it deprives its audience of valuable nonanalytic material. In spite of this, a considerable range of opinion is evident. If this is a representative cross section of psychoanalysts, a question not easy to answer, this book suggests that the field has continued to move farther along the course started by Loewald and Stone more than 30 years ago. That is, experiential and interpersonal factors of the patient-therapist interaction are generally considered more central to the curative process than they were formerly. Ultimately, the book is most instructive in showing how far we remain from being able to answer the most basic question of our work.

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Who Will Benefit From Psychotherapy? Predicting Therapeutic Outcomes, *by Lester Luborsky, Ph.D., Paul Crits-Christoph, Ph.D., Jim Mintz, Ph.D., and Arthur Auerbach, M.D. New York, Basic Books, 1988, 448 pp., $29.95.*

This book, coauthored by a dean of American psychotherapy research and a respected team of colleagues, is a definitive account of the psychoanalytic psychotherapy of 73 patients. Spanning two decades, the project represents a massive undertaking. Presented here are "the structural details of the Penn Psychotherapy Project, or the Penn study: the design, the evaluations, the patients, the therapists, the observers, the treatments, and the proposed data analyses" (p. 3). The study investigated, and the book reports, issues of great interest to both psychotherapy researchers and practitioners.

In this review I will emphasize the Penn study's findings and their import for the practice of psychoanalytic psychotherapy. The study's technical features, measurement methodology, and data analyses, topics of greater interest to psychotherapy researchers, will not be specifically addressed. Suffice to say that these features are well documented and impressively handled.

The book is a veritable gold mine of facts about patients, therapists, and treatment. However, for the purpose of a brief review, the study's findings may be conveniently, if reductionistically, grouped into three areas: the prediction of treatment outcomes by using pretreatment information; the frequency of different treatment outcomes; and curative factors associated with successful treatment outcomes.

The sample studied in the project was composed of subjects with mixed neurotic and personality disorders who, in most respects, typify outpatients seeking therapy. Data were collected over a 5-year period (1968–1973). The patients were seen in predominantly once-weekly individual psychotherapy (mean number of sessions=41), largely by psychiatry residents under clinical supervision.

Generally speaking, patients in the study achieved impressive treatment gains. Similar to results in previous psychotherapy studies (1, 2), about two-thirds (65%) of the sample were rated by therapists as "moderately to much improved" at the termination of therapy. Only 1% of the 73 patients were rated as worse (i.e., upset and disappointed with outcome) at termination of therapy. Moreover, a 7-year follow-up evaluation of 19 subjects confirmed the strength and durability of treatment benefits. Unexpectedly, a relationship emerged between psychotherapy gains and the reduction of physical symptoms, a finding with implications for future research.

With respect to determining who would benefit from psychotherapy, more than 80 carefully selected pretreatment predictors were examined in relation to measures of treatment outcome. Quite surprisingly, and much to the apparent chagrin of the researchers, success in predicting treatment outcomes from pretreatment information was dismal. Predictions, although positive in several respects, accounted for no more than 10% of outcome variance (correlations ranging from 0.20 to 0.30). Patient characteristics as assessed by a structured clinical interview were the best predictors; therapist and treatment characteristics added little.

Positive but weak predictors included scores from the structured pretreatment interview, similarity of patient and therapist, and length of treatment. Therapist characteristics such as demographic variables, years of clinical experience, supervisor ratings of clinical competence, or use of psychotropic medications failed to predict treatment outcomes. The method of assigning patients, either randomly or by therapist choice, was associated with treatment gains: therapist-selected patients fared better than those who were randomly assigned.

Following the "cold bath of limited success" in predicting outcomes, Luborsky and his colleagues microanalyzed the therapies of more- and less-improved patients. Eight "curative factors" emerged, four of which were quite potent. Two of these, reflecting dimensions of the patient-therapist relationship, will be briefly reviewed here.

The first curative factor—the patient's experience of a helping relationship—focused on the patient's view of the therapist as helpful and supportive. A second dimension of this factor was the perception of a sense of "we-ness" in the treatment process. In numerous papers that have emerged from the project, Luborsky and his colleagues have referred to this dimension as the "helping alliance." Correlations between helping alliance measures and composite outcome ratings were quite impressive ($r=0.58$, $p<0.01$).

A second curative factor—adequacy of the therapist's understanding—relates to the therapist's responses to the patient's main communications. This variable, essentially an operationalization of Freud's transference construct, involves two important dimensions: first, accurate formulation of the essence of the patient's communications by using the now well-known core conflictual relationship theme method and, second, the goodness of fit between therapist interventions and the patient's core conflictual relationship theme. Moderately strong positive associations were found between accurate formulation and response to patient core conflictual relationship themes and treatment outcome. These findings demonstrate a useful operationalization and validation of the cornerstone of psychoanalytic psychotherapy.

In a closing chapter and a massive appendix, Luborsky and his associates place their work in the context of four decades of previous psychotherapy research. This treasure trove of information brings the reader solidly into the center of the wide-ranging and bewilderingly complex enterprise of investigating psychotherapy outcomes. The book, in effect, consolidates what is currently known in the young science of empirical psychotherapy investigation.

Who Will Benefit From Psychotherapy? is, foremost, a compendium of information of value to professional psychotherapy investigators. It should also be of special interest to teachers, supervisors, and practitioners of psychoanalytic psychotherapy. The volume represents the epitome of applied clinical research. In conjunction with Luborsky's excellent *Principles of Psychoanalytic Psychotherapy* (3), a definitive and empirically researched rendering of psychoanalytic psychotherapy has been achieved.

Although sections of the book have all the reading excitement of the method section of a doctoral dissertation, the rationale for and presentation of statistics and methodology are illustrative and well done. Further, breaking the massive study into a logically connected series of mini-studies, each concisely summarized, makes the presentation less daunting to the reader.

The findings of the Penn study support the view that, despite therapists' belief in their prognostications, psychotherapy remains a sort of adventure, with an outcome that cannot, for now, be precisely foretold.

Who Will Benefit From Psychotherapy? should go far to silence critics who assail psychoanalytic therapy on the grounds that it is anachronistic and lacks proven efficacy. To the authors' credit, the Penn study demonstrates that Freud's seminal clinical discoveries may be reliably operationalized, efficiently taught, and empirically investigated and that their curative validity can be amply demonstrated.

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Mind-Body Therapy: Methods of Ideodynamic Healing in Hypnosis, *by Ernest Rossi, Ph.D., and David B. Cheek, M.D. New York, W.W. Norton & Co., 1988, 544 pp., $34.95.*

This book, coauthored by the unusual combination of an obstetrician-gynecologist and a psychologist, has two basic areas of special contribution. One concerns the advancements in the techniques and uses of hypnosis and, of equal importance, the newer, more scientific concepts of the mind-body relationships.

Hypnosis and other altered states of consciousness have been recognized for a long time. For a variety of reasons they have not been thoroughly accepted or studied by medicine. Most physicians in training are given little didactic information about hypnosis at any time. What we receive is often a sort of quasi-theoretical demonstration of a "hypnotic trance," often using a patient with a conversion symptom. The authoritative approach was used and the patient was told what would happen to his or her symptom or perhaps was required to remember something repressed and traumatic in nature. Unfortunately, the therapeutic results were at best temporary and at times the procedure was even harmful. Hypnosis was used during and following World War II, often supplemented by some type of barbiturate injection such as sodium amytal. In general, however, hypnosis did not receive any widespread recognition or use in medicine.

Interest in the concept of mind-body is as old as medicine itself. Some of Freud's earliest work was with hypnosis, but he subsequently abandoned it for free association. The newer hypnotic techniques are less authoritative and much more a team effort between the hypnotist and the patient; both are aware of the power and influence of the unconscious. Psychosomatic medicine also has gone through remarkable changes and refinements in the past few years. The focus is no longer on the fact that one influences the other but more on how this takes place. Our earlier view of synapses in the nervous system has grown rapidly with the increase in our knowledge of enzymes, hormones, autonomic functions, and the vast array of a "network" of interactions among various cells and their interactions with emotions and subsequently the maintenance of health, the positive or negative responses to trauma, and the invasion of foreign substances such as bacteria or viruses.

This book is divided into ten sections; space limitations in this review make complete coverage of all of these impossible. The authors begin with an explanation of "ideodynamic concepts in therapeutic hypnosis." The therapist and patient agree on the importance of the unconscious. They also agree that by careful, intuitive questioning, areas of the unconscious can be made conscious and understood and worked through. It began with the use of a pendulum held by the patient and used to answer either in the affirmative, the negative, or, "I'm not ready to know the answer consciously yet," depending on which way the patient moved the pendulum. This went on to the use of fingers instead of the pendulum, again with the same answers—yes, no, or, "I'm not ready yet." Varying degrees of hypnosis were involved. Simply put, the finger signals dealt with the unconscious and verbalization and head nodding dealt with the conscious. Not infrequently, patients were surprised to find contradictions between these two and became increasingly curious to know more.

Considerable discussion is devoted to our newer knowledge of the factors involved in the psychobiology of mind, memory, and behavior. The term "informational substances" is used to refer to those substances which are widely spread through the nervous system and are important in stimulating or modifying receptors elsewhere in the body. From this comes the concept of a "network" with an infinite number of potential responses.

Of practical importance is the elaboration of general anesthesia as commonly used in surgery and the fact that a fully anesthetized patient may still have a functioning auditory system, so that the words said by operating room personnel may be retained in the unconscious of the patient but, as the authors say, in a "childlike" manner. This may lead to misinterpretations and alter the course of surgery and postsurgery recovery. What is retained is not necessarily an accurate unconscious memory of statements made but, rather, a memory of the meaning of the statements for the patient.

The book has many clinical examples, usually verbatim statements. Many summarized specific suggestions are made in heavily outlined boxes. In one chapter, "'Emotional Factors in Persistent Pain," the authors discuss the unconscious factors often involved in patients with pain who in spite of every possible therapeutic effort do not improve. This may follow a minor trauma long healed or a chronic problem such as phantom limb, tic douloureux, or reflex sympathetic dystrophy. Physicians may become discouraged or angry. The authors point out that "neurosurgical attempts to relieve pain with problem patients are sometimes comparable to dynamiting the power house to turn off the kitchen light." An example is "manipulative pain states," where the origin is a disease or injury that alarmed or injured an important person in the patient's life. Subsequent pain may recur when there are hostile feelings toward that person and eventually in response to any emotional difficulty caused by anyone. Careful ideodynamic hypnosis by a trained therapist is often useful, but in the hands of a poorly trained therapist it can be disastrous.

Given that one of the authors is trained in and practices obstetrics and gynecology, one would expect and, indeed, one finds considerable discussion of emotional problems in a variety of conditions seen in this specialty. Such things as habitual abortion, sexual dysfunction, and vaginal infections are covered with many illustrative case histories.

The authors provide suggestions at the end of each section for further research projects. They are aware that some of their material does not fulfill true scientific research and why such research is often difficult to do in this field. Anyone can say that the patient may have gotten well anyway. The authors also make a point regarding the degree of success a therapist may have with ideodynamic work with patients. This, of course, concerns the personality of the therapist—his or her view of the technique and belief in its capacity. For example, it is pointed out that Dr. Cheek has a capacity for quickly establishing a positive, trusting, optimistic, and cooperative attitude in many patients. This is another difficult concept to prove, but most of us in medicine recognize it when we see it. Empathic physicians with these qualities become the doctors' doctor.

This is a thought-provoking, informative, well-written book in an area that has a large future but has so far often been ignored or dismissed. It is to be recommended to all physicians and health workers but is a must for psychiatrists.

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STRESS

The Psychology of Fear and Stress, 2nd ed., *by Jeffrey Alan Gray. New York, Cambridge University Press, 1988, 422 pp., $75.00; $22.95 (paper).*

This book is intended to be a comprehensive analysis of the psychology of fear and stress for behavioral scientists. The first edition was published in 1971, and there has been considerable research in the intervening 17 years. This second edition is well warranted. That it is well written is no surprise, since the author is a leader in the field, having come forth with extremely interesting theories about the mediation of anxiety and fear responses in the brain.

The author has a long-range goal of mapping the mind-brain or, at the least, the behavior-brain connection as it focuses on issues of anxiety. The text pays careful attention to behavior under different experimental conditions, especially in research with animals, where the brain can be studied either through electrophysiology or in pathological specimens. This focus on the biology of anxiety makes this an important book for all who would do scholarly work on the antianxiety agents and on the link between psychosocial and biological theories of the anxiety disorders. It is also a very good review for beginners in this field.

For the practicing psychiatrist this volume may offer an update on cognitive neurosciences and animal experimentation as well as various theories of emotion (not just anxiety) in their physiological and conscious correlates. Because the psychodynamic perspective on anxiety is not dealt with, however, the text has little direct relevance to clinical practice. If psychology can be understood as including unconscious mental processes examined in their own right, as structures of meaning, and not simply as the information processing that is epiphenomenal to the activities of neurons, then the book might better be titled *The Neurobiology of Fear and Stress.* Although the book is somewhat difficult to read because it consists of many descriptions of important experiments in the field, the author does not simply summarize; he has organized the book in an orderly and systematic way and gives his own lucid opinions and theories. There are frequent references to everyday human experiences of emotion that help the reader relate experiments to clinical issues.

My caveat regarding the book's neurobiological focus notwithstanding, this is an intelligent and successful work, an essential "first textbook" on the basic science issues. The emphasis on literature before 1980 is completely justified, and the author has done considerable work to make the second edition definitive.

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Handbook of Life Stress, Cognition and Health, *edited by Shirley Fisher and James Reason. New York, John Wiley & Sons, 1988, 713 pp., $132.00.*

Like the science of physical anthropology, psychosomatic medicine has long searched for its own version of the missing link—that crucial piece of evidence or leap of insight to transform ideas about stress and illness into an elegant, unified theoretical whole. As the title implies, this volume places a central emphasis on the role of cognition—the set of personal assumptions, attributions, and meanings about oneself and the world—as crucial mediating influences between stress and healthy adaptation versus stress leading to mental or physical illness.

The work is lengthy (the table of contents alone comprises 11 pages) and serves both as a review of current studies on stress and illness and as a repository of original theoretical models. Section one examines specific stressful events and contexts such as expectant parenthood, bereavement, impending surgery, and unemployment. Section two examines specific disorders such as coronary artery disease, cancer, diabetes, anorexia nervosa, and depression to adduce the role of stressful life events in the genesis or outcome of these conditions. Section three focuses specifically on the cognitive processing of life experiences as a contributor to mastery, coping, adaptation, anxiety, depression, and personality style. Section four offers several models of the relationship of assumptive worlds and human information processing to psychobiological health and illness. Section five discusses intervention strategies to achieve coping and mastery of stress.

The book is full of stimulating ideas, as the following highlights will indicate. A chapter entitled "Psychobiological Interaction in Depression" examines the means by which separation, helplessness, and "social defeat" (i.e., loss of status) create personal meanings and internal mental representations that, in turn, activate psychobiological response patterns in the brain. The brain mechanisms governing these response patterns may have their origin in reptilian life forms, as illustrated by the observation that high-status lizards lost their brightly colored appearance and died soon after losing rank in their social hierarchy (p. 559). The author, Paul Gilbert, hypothesizes that neuropsychological responses to stress may be influenced by baseline hormonal states, which themselves may be determined by social factors such as the presence of a confiding relationship. Internally generated images and appraisals of the symbolic meaning of events trigger physiological processes, including endogenous depression: "Just as we can create sexual fantasies in our heads and then experience a precise pattern of physiological arousal, there is no reason to assume that images of ourselves as defeated, unloved, abandoned or rejected cannot also invoke powerful physiological effects" (pp. 573–574). In further refining psychobiological models, subsequent authors propose that the pathway from life event to illness occurs through one or more of three specific mechanisms. In the wake of stressful life changes, individuals may 1) be physically exposed to new or increased antigens or pathogens, 2) exhibit consequent behavioral changes that increase risk of injury or malfunction, or 3) experience altered mental or physical states such as worry, arousal, or preoccupation. Worry, or "ruminative activity" (p. 599), results in hormonal changes (increases in cortisol and catecholamines), which in turn lead to functional abuse of organs (ulcers, heart disease) and immunosuppression (infection, malignancy).

In the section on coping with stress, one learns about factors related to the ability to resist stress, including physical health, personality, social support, and the ability to maintain meaningful activity in the face of traumatic social change. In "Confiding Traumatic Experiences and Health," James W. Pennebaker observes that in contrast to "acceptable" stressors such as the death of a spouse or unemployment, some events, such as rape or combat service in an unpopular war, are socially stigmatized and thus difficult to disclose even when they occur in individuals who enjoy strong social networks. The inhibition of thoughts and feelings about traumatic events is physiologically taxing and can lead to stress-related diseases. Disclosure of such thoughts and feelings is beneficial because it relieves the individual of the physiological and cognitive onus, thereby alleviating autonomic overactivity, obsessive thinking, self-imposed social isolation, and attendant anxiety states.

This book is an important one for several reasons. The relationship between psychological stress and biological illness has received steadily increasing attention among scientists, clinicians, management in the private sector, and the general public. As Shirley Fisher observes, "What used to be thought of as psychosomatic medicine is fast becoming the domain of modern medical science" (p. xxiii). This work, although more a textbook than a handbook, provides stimulating, provocative reading from a refreshingly biopsychosocial point of view. It will aid clinicians in their treatment of patients experiencing life stresses. In the quest for the missing link of stress and illness theories, it does not deserve to become just another fossilized tome.

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Resilience: Discovering a New Strength at Times of Stress, *by Frederic F. Flach, M.D. New York, Fawcett Columbine, 1988, 270 pp., $16.95.*

Our notions of stress and its sister concept resilience may be so diverse as to defy coherent description. In daily speech, "stress" has become an overworked cliché. We use it to identify those external evils we deplore but cannot change: midlife crises, teenage pregnancy, drug abuse, layoffs, acid rain, the threat of nuclear holocaust—the list is as long and as numbing as a stress management seminar. On the other hand, psychological resilience is an emerging concept not yet served by generally accepted theories. Frederic Flach's *Resilience* is therefore a timely and useful addition to this growing body of thought.

Dr. Flach is a psychiatrist and author who practices in Manhattan. He is an adjunct associate professor of psychiatry at New York Hospital–Cornell Medical Center, and he has written previously on depression and on marriage. This work is intended for both a lay and a professional audience. It examines those features of ourselves, our families, and our larger social networks which promote a creative response to the events that sometimes threaten the fabric of our lives. Its thesis is that resilience lies in one's ability to experience fully the painful disorganization and emotional tumult which these crises bring in order to emerge with a higher level of personal integration and with a deeper appreciation of the values that guide one's life. In many respects the essence of this message is not really new, yet it remains very relevant today and deserves serious consideration.

Resilience begins with a brief theoretical description of the process of emotional disruption and reintegration, arguing that homeostatic functioning, at whatever cost, may not always serve one's long-term needs. The concept of a "bifurcation point"—a phrase taken from the work of the physicist and systems theorist Ilya Prigogine—is introduced as a moment when extreme change may occur and lead either to higher organization or to greater disorganization—chaos. Next follows an extended discussion of the personal crises that await us all as we traverse the life cycle. Despite the aura of systems thinking, most psychiatrists will encounter little that is new here. The third part of the book deals with the origins of resilient personality functioning, including its biological roots, its dependence on a sense of personal competence and self-esteem, and the central role of creative thinking and adaptive problem solving. Dr. Flach has explored the relationship between resilience and creativity in an earlier publication (1). I found this section of the book to be the most inherently interesting and wish very much that the author had expanded it. Finally, this book discusses the not-so-small matters of the interpersonal, social, and spiritual aspects of resilience that can play a major role in an individual's response. These topics are not the traditional territory of psychiatry yet are vital considerations in understanding resilience. This discussion is valuable for its forthright and nonpartisan approach.

I enjoyed reading this work, which is written with a personal, open, and graceful style. In speaking to a general audience however, I feel it also skirts some of the more fascinating and difficult aspects of its topic. To pursue an example, one may ask what distinguishes one emotional disruption from another? How does one know when a disruption is serving the development of the self and when it is not? Often, I submit, one knows only in retrospect. Here the clinical debate about adolescent turmoil comes to mind. Another broad area that might have been more fully explored concerns the relationship between experiences of emotional turmoil and disruption and the capacity for artistic creativity. In this century T.S. Eliot's great poem *The Waste Land* (2) makes this issue a central concern.

Finally, it would have been helpful to have a more complete discussion of what characterizes the states of ongoing disruptions and disorganization we call major mental illness—certainly not just the stigma of diagnostic labels, as Dr. Flach implies. Furthermore, what are the sources of resilience in seriously disturbed personalities? Can resilience in fact serve to continue dysfunctional patterns of adjustment? What makes it possible for some people to be highly creative and productive in certain areas of their lives while other areas remain a shambles. In struggling more intimately with some of these paradoxes, I feel Dr. Flach might have written an even more illuminating book.

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Reprints of Book Forum reviews are not available.

Rapid Detoxification From Opioid Dependence

SIR: Detoxification from opioid dependence usually requires at least 14 days, but the time can be substantially reduced by precipitating withdrawal with opioid antagonists such as naloxone (1). While this approach is quite promising, the withdrawal symptoms produced by the antagonist can be severe and inadequately controlled by nonopioid agents such as clonidine (1). To further decrease the severity of this withdrawal, we have explored the use of buprenorphine, a partial agonist, as a transitional agent between agonists (e.g., methadone or heroin) and antagonists (e.g., naltrexone) (2). The transition from either methadone or heroin to buprenorphine has been quite successful, with good retention and only minimal withdrawal symptoms (2). However, detoxification from buprenorphine and initiation of naltrexone has met little success because of mild but prolonged withdrawal symptoms (3). To reduce the duration of this buprenorphine withdrawal period, we have attempted antagonist-precipitated detoxification on the basis of previous work suggesting that 10–16 mg of naloxone are required for precipitating withdrawal (4). Using a dose of naloxone (about 32 mg) high enough to ensure precipitation of buprenorphine withdrawal, we tested a rapid detoxification procedure in a blind, placebo-controlled design.

Five opioid-addicted patients who had been taking buprenorphine, 3 mg sublingually, for 1 month as outpatients had their buprenorphine abruptly discontinued with blind substitution of placebo and were enlisted in a placebo-controlled, double-blind challenge with intravenous naloxone, 0.5 mg/kg. The naloxone was given over a 20-minute period in a 10-mg/ml solution. Vital signs and withdrawal symptoms were monitored at baseline and every 30 minutes for 3 hours with the 15-item Abstinence Rating Scale (5), on which scores can range from 0 to 45.

Naloxone precipitated significant opioid withdrawal symptoms in these five patients. The mean±SD symptom score (5±1.3 at baseline) increased to 13±2.2 60 minutes after the start of the infusion (Time by Challenge, $F=3.2$, $df=5, 40$, $p<0.02$). For 3 hours the severity of withdrawal symptoms remained relatively constant, with a peak score of 15±4.1 between 120 and 180 minutes. Peak mean blood pressure also showed a significant change during the naloxone challenge compared to placebo, with a mean±SD rise of 10.5±3.0 mm Hg ($t=5.8$, $df=4$, $p<0.005$). This blood pressure change is comparable to the change noted in our previous work using antagonists in methadone-maintained patients, whose mean blood pressure rose 13±12 mm Hg (5). However, the severity of withdrawal for the current five patients was about two-thirds the severity for the methadone patients (mean±SD Abstinence Rating Scale score=22±9.3) and less than a third of the full possible score of 45. Furthermore, 5 hours after this naloxone challenge, withdrawal symptoms were at baseline levels, and oral naltrexone was given at a dose of either 12.5 mg or 25 mg without precipitating further withdrawal symptoms. The following day the naltrexone dose was doubled, which resulted in some sleep difficulty but no major withdrawal symptoms. Two patients continued to take full maintenance doses of naltrexone (50 mg/day) for the next month, but the other three discontinued naltrexone treatment.

The strategy of antagonist-precipitated withdrawal has been successfully used for rapid detoxification from a variety of opioid agonists (1) and now appears to be a feasible approach for buprenorphine-treated patients, if a sufficiently high dose of naloxone is given. The buprenorphine withdrawal syndrome was milder than antagonist-precipitated methadone withdrawal, suggesting a partial resetting of the opioid receptors by the antagonist activity of buprenorphine (1, 2). Since part of the difficulty in keeping all five patients on the naltrexone regimen was the withdrawal symptoms that were initially precipitated by the use of naloxone, pretreatment with clonidine or a similar agent might substantially improve the chances of successfully maintaining patients on a naltrexone regimen by ameliorating these symptoms (5). In summary, transitions from full agonists to buprenorphine and now from buprenorphine to full antagonists have been demonstrated, which suggests that further research on this clinical approach to detoxification from opioids be pursued (2).

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Illicit Substance Use by Acutely Psychotic Patients

SIR: Evidence is accumulating that substance abuse is common among psychiatric patients and probably contributes to exacerbations of illness (1, 2). As part of a larger study, we monitored the use of urine drug screens for 100 consecutive patients admitted to a Veterans Administration psychiatric facility. The admitting physician ordered urine drug screens on the basis of his clinical judgment. Drug screens were ordered for 38 of the patients admitted. Of these 38 screens, 12 (31.6%) were positive, and eight of these 12 were positive for cocaine. Six of the cocaine-positive urine screens were obtained from individuals who were psychotic upon admission.

Approximately 1 week after admission to the unit, all patients were interviewed with structured clinical interviews about their recent and past drug use. Five of the 12 patients with positive urine drug screens denied current drug use upon admission and upon interview 1 week later. All five of these patients had urine drug screens that were positive for cocaine; two were additionally positive for cannabis. Three of these patients had diagnoses of schizophrenia—one had chronic undifferentiated schizophrenia and two had paranoid schizophrenia. The remaining two patients who denied drug use in spite of positive urine drug screens had diagnoses of atypical psychosis and adjustment disorder. Of the 12 positive urine drug screens, eight were obtained from individuals who were psychotic upon admission, five of whom had had a previous diagnosis of schizophrenia.

It appears that the current cocaine/crack epidemic has had an impact on psychiatric patients. In view of the potential psychotomimetic properties of cocaine, this information argues for the usefulness of urine drug screens, particularly for acutely psychotic patients. Even if a patient has a documented preexisting psychotic disorder, substance abuse is apparently common and may be an important contributing factor to relapse. In addition, particularly for the paranoid psychotic patient, a urine drug screen may provide valuable information that the patient is unwilling or unable to provide.

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Pathophysiology of Obsessive-Compulsive Disorder

SIR: Obsessive-compulsive disorder is characterized by recurrent intrusive and disturbing thoughts (obsessions) and/or repetitive, stereotyped behaviors that the person feels driven to perform but recognizes as irrational or excessive (compulsions). The predominant hypothesis regarding the neurobiological basis of this disorder posits a dysregulation of serotonergic function. This hypothesis is largely based on evidence that potent inhibitors of serotonin reuptake, such as clomipramine and fluvoxamine, are particularly effective in the treatment of obsessive-compulsive disorder. Despite the clear efficacy of these agents in many cases, however, few patients become entirely symptom free, and as many as one-half of these patients are clinically unchanged after adequate treatment trials with serotonin reuptake inhibitors. The role that other neurotransmitter or neuropeptide systems may play in the pathophysiology of this group of treatment-resistant patients warrants investigation. The following case suggests that alterations of dopaminergic function may contribute to the pathophysiology of certain subtypes of obsessive-compulsive disorder.

> Mr. A was a 45-year-old man with a 30-year history of disabling fears of contamination and associated compulsive washing rituals as well as a need for orderliness and symmetry. In addition, he had had a left shoulder tic since the age of 8. He experienced an acute exacerbation of these phenomena following the nasal insufflation of cocaine. Fifteen minutes after ingesting about 150 mg of cocaine for the first time, he noticed the onset of compulsive grooming rituals, repetitive handwashing because of a fear that his hands were contaminated with chemicals, symmetrical arranging of his personal belongings, and increased frequency and amplitude of left shoulder jerks. The crescendo pattern of these obsessive-compulsive and tic phenomena temporally coincided with cocaine-induced euphoria, both reaching a peak approximately 30 minutes following drug ingestion. Within 2 hours, the exacerbation of symptoms and the elevated mood returned to baseline. Mr. A reexperienced nearly identical exacerbations twice more within the next 3 weeks upon repeated nasal ingestion of cocaine. Although the patient had imbibed alcohol and smoked marijuana in the past, the only effect of those substances had been a mild reduction in anxiety. In addition to obsessive-compulsive disorder, the patient met the *DSM-III-R* criteria for chronic motor tic disorder. Subclinical obsessive-compulsive disorder was identified in Mr. A's father, and his brother was diagnosed as having paranoid schizophrenia. At the time of cocaine ingestion, Mr. A's medication regimen consisted of imipramine, 200 mg at bedtime.

Cocaine inhibits the reuptake of dopamine and norepinephrine in the CNS. Mr. A had been treated with the tricyclic antidepressant imipramine—which inhibits reuptake of norepinephrine and serotonin but not dopamine—without any exacerbation of the shoulder tic or obsessive-compulsive behaviors. Furthermore, existing data suggest that increased noradrenergic turnover does not, by itself, contribute to obsessive-compulsive symptom formation or exacerbation (1). Thus, it is likely that cocaine's facilitative effect on dopaminergic function contributed to the marked worsening of Mr. A's symptoms.

Two recent reports (2, 3) have described cocaine-induced exacerbation of motor and phonic tics in patients with previously diagnosed Tourette's disorder. Although the pathogenesis of Tourette's disorder is unknown, postsynaptic dopamine receptor supersensitivity has been postulated (2). Similarly, the development of obsessive-compulsive symptoms following stimulant therapy for attention deficit disorder (4) suggests a dopaminergic contribution to the pathophysiology of obsessive-compulsive disorder.

To our knowledge, this is only the second account of cocaine-induced exacerbation of obsessive-compulsive disorder (5). However, it is the first report to suggest that cocaine's facilitative effect on dopamine function might underlie the worsening of obsessive-compulsive symptoms. Additional studies investigating the relative contributions of, and interactions between, brain dopamine and serotonin systems are necessary to identify neurobiologically distinct and clinically meaningful subtypes of obsessive-compulsive disorder.

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Higher Frequency of Separation Anxiety in Panic Disorder Patients

SIR: Several authors have reported a higher frequency of childhood separation anxiety in patients with various anxiety disorders (1, 2). However, some studies have questioned these findings (3). We reported a greater frequency of childhood separation anxiety in panic disorder patients than in normal control subjects but not depressed patients (4). Now we have examined possible differences between men and women in a bigger sample.

We studied 100 panic disorder patients (56 with various degrees of agoraphobia) and 100 normal control subjects. There were 40 male patients (mean±SD age=34.1±6.8 years), 60 female patients (32±8.6 years), 50 male control subjects (29.2±6.0 years), and 50 female control subjects (29.7±5.8 years). This sample included 35 panic disorder patients and 30 control subjects used in our previous study (4).

The patients were diagnosed according to the *DSM-III* criteria for panic disorder. Subjects completed a nine-item questionnaire representing the *DSM-III* criteria for separation anxiety disorder of childhood or adolescence (until the age of 16). A positive history of childhood separation anxiety was defined as three items present for at least 2 weeks.

Twenty-nine patients (nine male and 20 female) and six control subjects (four male and two female) met the criteria for childhood separation anxiety. There was a significant difference in frequency of childhood separation anxiety between the patients (29%) and the control subjects (6%) ($p<0.00001$) (all tests of significance were by Fisher's exact test, two-tailed). The difference in frequency of childhood separation anxiety between male patients (22.5%) and male control subjects (8%) was not significant, but the difference between female patients (33.3%) and female control subjects (4%) was highly significant ($p<0.0001$). The differences in frequency of childhood separation anxiety between male and female patients, between patients with agoraphobia (17 of 56, 30%) and without agoraphobia (12 of 44, 27%), and between male (six of 24) and female (11 of 32) patients in the agoraphobic group were not significant.

These findings confirm our previous findings (4). Even though a history of childhood separation anxiety was more frequent in the women in our sample, the difference was not statistically significant. These findings are somewhat different from those of Gittelman and Klein (1), as we did not find a significant association between childhood separation anxiety and agoraphobia in women. Only 30% of our patients with some agoraphobia had a history of childhood separation anxiety, which is less than the percentage in Gittelman and Klein's study (50%). The difference may be accounted for by the less stringent diagnostic criteria in our study, since our patients met just the *DSM-III-R* criteria for agoraphobia, which include panic disorder with mild symptoms of agoraphobia.

Even though this study had the limitations of any retrospective study, our finding of a significantly higher frequency of childhood separation anxiety among panic disorder patients supports other studies' findings that there is a possible link between childhood and adult anxiety disorders.

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The Case for the Diagnosis of Organic Catatonic Syndrome

SIR: The organic mental syndromes section in *DSM-III-R* includes 11 main categories. Organic anxiety syndrome, which was only mentioned in the text and not included as a category in *DSM-III*, is the new category of organic mental syndromes in *DSM-III-R*. However, one major omission remains—that of organic catatonic syndrome, the inclusion of which would make the coverage of organic mental syndromes comprehensive.

It is now 13 years since Gelenberg's excellent review of the catatonic syndrome (1) appeared in the literature. It emphasized the multiple underlying causes of the syndrome. Another article published in the same year (2) showed that more than 16% of patients with one or more catatonic symptoms had organic brain disease, and less than 8% of these patients met research criteria for a diagnosis of schizophrenia.

The impact of these articles (and other research) on *DSM-III* was that the diagnosis of catatonic schizophrenia required the presence of not only catatonic features but also characteristic schizophrenic phenomena. This was a step forward from the earlier editions of *DSM*, where the presence of catatonic features meant a diagnosis of catatonic schizophrenia. Also, it was recognized that catatonic symptoms can occur in affective disorders, and their presence was included as "mood-incongruent psychotic features" in the diagnostic criteria for manic episodes. (However, catatonic symptoms are not included in the criteria for major depression in *DSM-III-R*.) This still left a large number of cases in which the catatonic symptoms were the result of underlying organic illness (3). A diagnostic category for these cases is missing from *DSM-III-R*.

If we follow the decision tree for differential diagnosis of psychotic symptoms in *DSM-III-R* (appendix B) to find a diagnosis for catatonic symptoms ("catatonic stupor or excitement"), we are referred to the organic decision tree if an "organic factor that initiated or maintained the disturbance has been established." However, the word "catatonic" does not appear at all in the decision tree for differential diagnosis of organic mental disorders. It can only be inferred that the presence of such a diagnostic situation would lead to a diagnosis of either organic mental disorder not otherwise specified or delirium, if the catatonic symptoms "occur *exclusively* during periods of delirium."

On referring to the text on delirium (the diagnostic criteria for delirium do not mention catatonic features), we find that in delirium there may "even [be] certain features resembling catatonic stupor" (p. 101). Clearly, this description is not enough for a diagnosis of organic catatonia. For example, catatonic syndrome secondary to neuroleptic administration, globus pallidus lesions, diencephalic lesions, frontal lobe disorders, or periodic catatonia does not usually present with delirium (in contrast to limbic encephalitis, which does).

Organic mental syndrome not otherwise specified is the only remaining category in which such cases could be placed. There is no mention of catatonic features in the criteria for this category, nor would that be enough. We strongly feel that organic catatonic syndrome should be included as a separate category under organic mental syndromes in *DSM-IV*. This will facilitate clinical diagnosis and will help standardize future research in this important area.

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Fourier's View on Homosexuality

SIR: Although Freud never claimed that all of his ideas were original, the relationship between unconscious homosexuality and paranoia is generally considered to have been his personal discovery. The passage by Charles Fourier quoted here is, therefore, of historical interest. There is no evidence (e.g., citations in his writings or books in his library) that Freud was familiar with the work of Fourier.

Charles Fourier was a French idealist social reformer and philosopher who lived from 1772 to 1837. He was an isolated worker in his time, and his writings are now generally considered to be of only minor historical importance. The following quotation is from a translation by Susan Hanson of Fourier's "New Theory of Society."

> Dame Strogonoff, a Muscovite princess, seeing herself grow old, was jealous of the youth and beauty of one of her slaves. She frequently had her tortured and she herself often stuck her with pins. What was the real motive of her cruelty? Was it truly jealousy? No. It was lesbianism. Without knowing it, this lady was a lesbian, in love with the beautiful slave whom she tortured. If someone had acquainted Mme. Strogonoff with the idea of lesbianism and had arranged a reconciliation between herself and her victim, these two would have become passionate lovers. But the princess, failing to consider the idea, fell into a counter-passion, subverting her true feeling and persecuting the object, with whom she would have found pleasure. Her rage was proportionately greater as the repression came from a prejudice which, hiding from this lady the true nature of her passion, did not allow its ideal development. (1)

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Fluoxetine and Extrapyramidal Side Effects

SIR: We are writing in support of some preliminary observations by Jeffrey L. Tate, M.D. (1) on unexpected side effects of fluoxetine on extrapyramidal symptoms. Fluoxetine, in doses ranging from 20 to 60 mg/day, has been used since January 1989 in our neuropsychiatric research unit for 28 patients with major depressive disorders.

The patients were monitored in a blind manner with an assessment scale of extrapyramidal symptoms derived from the Colombia Rating Scale (2), which is currently used in pharmacological studies of Parkinson's disease (23 items are scored from 0 to 4, with a maximum disability score of 92; a score above 15 indicates functional disability).

Five patients showed a deterioration of their bradykinesia and rigidity subscores after introduction of fluoxetine. In three patients receiving 20 mg/day, the associated treatment (prednisone, 10 mg/day for one; pimozide, 2 mg/day, and a previous injection of fluphenazine decanoate, 37.5 mg, 4 weeks earlier for the others) led to difficult interpretations of the effect of fluoxetine. In two cases, reported here, fluoxetine was the only drug prescribed.

> Ms. A, a 47-year-old woman with a diagnosis of borderline personality disorder, entered our unit during a major depressive episode that had lasted for 2 months. Two months before, her physician had canceled her prescriptions for haloperidol, 5 mg b.i.d., and benztropine, 2 mg b.i.d., which she had been taking for some months.
>
> Ms. A's baseline parkinsonian score before starting fluoxetine was 6, and her symptoms consisted essentially of discrete asymmetrical cogwheel rigidity. At a dose of 40 mg/day of fluoxetine, she began to complain of clumsiness and restlessness; her face took on a masklike look and her gait was shuffling.
>
> The cogwheel rigidity became obvious to the house officer as the patient's parkinsonian score increased to 22, and the fluoxetine was stopped. Within 2 weeks after the fluoxetine was withdrawn, Ms. A's parkinsonian score returned to the baseline level.

Ms. B, a 45-year-old woman with a diagnosis of schizoaffective disorder, was hospitalized for major depression of the melancholic type with severe motor retardation and anxiety. There was no plastic or cogwheel rigidity at the initial blind assessment made by our neurologist. Her baseline parkinsonian score was 7.

At a dose of 20 mg/day of fluoxetine, Ms. B developed an action tremor and akathisia, and a discrete cogwheel rigidity was noticed. At a dose of 40 mg/day, a fine resting tremor of the mouth, of the "rabbit syndrome" type, appeared, and obvious parkinsonian bradykinesia and rigidity, more apparent in the left than the right limbs, markedly disabled the patient. Her parkinsonian score increased to 29. Bromocriptine was given for a short period during the withdrawal of fluoxetine to achieve a correction of the parkinsonian symptoms.

Our vigilant attitude toward fluoxetine has developed from unpublished observations of the deterioration of parkinsonian patients receiving selective serotonin reuptake inhibitors that have been tried (Upstene) or are currently in use (Floxyfral) in France. From our observations we can infer that fluoxetine has an indirect dopamine-blocking effect, at least in some persons at risk. An explanation could be that the increased serotonergic activity of the raphe nuclei projections on nigral cells may have deleterious effects on dopamine turnover in persons with poor nigrostriatal dopamine reserves.

This explanation, if confirmed by further clinical observations, would imply that serious caution should be exercised when using selective serotonergic drugs in the treatment of depression associated with Parkinson's disease. Further studies of the concomitant use of neuroleptic drugs and pure serotonin-reuptake-blocking drugs are also necessary.

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SIR: In a recent letter to the Editor (1), severe extrapyramidal symptoms were reported in a patient who had recently discontinued haloperidol and was currently taking fluoxetine. I recently observed a patient who developed severe, generalized muscular stiffness in association with fluoxetine.

Ms. A was a 38-year-old woman with cerebral palsy and a long-standing history of recurrent unipolar major depression. Other than her cerebral palsy, she had no known neurological disorder. Her depressive symptoms had been under stable control for the preceding 2 years on a regimen of trazodone, 150 mg h.s., and the muscular spasms associated with her cerebral palsy had responded partially to cyclobenzaprine, up to 30 mg/day, supplemented by occasional doses of aspirin and ibuprofen.

During hospitalization for evaluation of a left bundle branch block, the patient's cyclobenzaprine and trazodone were discontinued, and haloperidol was added for treatment of a myoclonic movement disorder (in the presence of a normal EEG) that was associated with her cerebral palsy. She derived significant benefit from the haloperidol, 1 mg/day, which she took for 5 consecutive days without extrapyramidal symptoms or exacerbation of the spasticity associated with her cerebral palsy.

Three weeks after discontinuing trazodone, Ms. A suffered a recurrence of depressive symptoms with suicidal ideation, prompting the addition of fluoxetine, 20 mg/day. Four days later, she reported severe, generalized muscular stiffness, particularly prominent in her arms, legs, and back, which increased in severity over the ensuing 4 days. During that 8-day period, she had taken haloperidol, 1 mg/day, on 5 days. Fluoxetine was discontinued and trazodone, 100 mg h.s., was reinstituted. Within a week her spasticity had improved substantially, and within another week it had diminished to myoclonic movements. On 2 days during the latter week she took 2 mg of haloperidol; on both days her myoclonic movements improved after she took the haloperidol, and she suffered no increased muscular stiffness.

Heterocyclic antidepressants have only rarely been associated with neurolepticlike extrapyramidal symptoms (2, 3). Ms. A did not experience increased muscular stiffness until fluoxetine was added; moreover, her muscular stiffness remitted within 12 days after discontinuing fluoxetine (consistent with the 7- to 15-day half-life of norfluoxetine, the active demethylated metabolite of fluoxetine) and did not recur despite continued treatment with haloperidol. It is therefore possible that her muscular stiffness was induced by fluoxetine or resulted from a fluoxetine-haloperidol interaction. Like Dr. Tate's case (1), this case suggests that fluoxetine may, by itself or in combination with neuroleptics, induce or exacerbate extrapyramidal side effects.

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Psychotherapy With Schizophrenic Patients

SIR: The study by Leonard L. Glass, M.D., and associates (1) on the effectiveness of dynamic explorative individual therapy in the treatment of schizophrenia fits well with my own clinical experience. I have been working for the past 10 years to develop a variation of intensive psychoanalytic psychotherapy for a selected group of chronic psychotic patients, in conjunction with antipsychotic medication and rehabilitation programs.

The finding that greater skill of the therapist was correlated with better outcome was interesting, as it has seemed to me also that the therapist's skill is one of the most important predictors of success. I would suggest that in addition to sound understanding of psychodynamics and attunement to the patient's underlying concerns, the therapist's silent, systematic attention to his or her own countertransference is vitally important in this type of therapy—something that is almost impossible to measure objectively. The fact that the majority of the therapists in the study by Dr. Glass and colleagues had had personal psychoanalyses suggests the authors' awareness of this factor.

Another predictor of outcome that was not addressed in their study is the pretreatment qualities of the patient. It is my hypothesis that there is a subgroup of chronic psychotic patients who can participate in and benefit from explorative individual therapy. If this is true, it is important to be able to identify what qualities these patients have that could predict better outcome. My clinical impression is that motivation to remain nonpsychotic and to achieve social and vocational goals is one such quality. Kernberg (2) suggested that psychotic patients may "seal over" and then present an underlying personality organization at a psychotic, borderline, or neurotic level. Higher-level personality organization might be an indication for explorative therapy. Neither the amount of previous treatment, the chronicity of symptoms, nor the level of positive symptoms appears to me to predict outcome.

The finding that at 2 years there is reduced denial of illness, reduced retardation and apathy, and increased anxiety/depression also fits well with my clinical experience. The focus in the earlier stages of treatment is often on the chronic, rigid characterological defenses that inhibit underlying affects, both in the transference and in the patient's current life. If these defenses are successfully loosened, there is less apathy and retardation but heightened anxiety and often a stormy, more symptomatic period. One frequently sees patients who, after 2 years, can consistently explore underlying ambivalent affects within the therapeutic hours, but because of the increased anxiety generated, they appear more symptomatic in social relationships with friends and family. Thus, it is not surprising to me that only marginal improvement in global psychopathology is found after 2 years. If the therapy can hold together through the stormy ambivalent period, a new stage will often emerge in which the patient has internalized enough of the soothing qualities of the therapist to modulate anxiety between sessions and to begin to express more integrated affects in day-to-day life. This is the stage of treatment in which rehabilitation and improvements in vocational, social, and interpersonal skills begin to be possible. I suggest that it is important to extend the type of study Dr. Glass and associates did to 3–5 years to accurately measure change in global psychopathology.

Since it is commonly taught in psychiatric training (3) that explorative individual therapy is ineffective and contraindicated for schizophrenic patients, studies such as this one are vitally important to define the parameters and outcomes for a group of patients who may be otherwise doomed to a life of misery.

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Reporting Seizures and Blackouts

SIR: In a letter to the Editor (1), Kenneth A. Nakdimen, M.D., inquired, "How can we know whether we are seeing no, few, or many cases of multiple personality if we are not even screening for, let alone evaluating for, this disorder?" He urged asking patients, "Have you ever gone blank or had a memory gap, so that there were minutes or hours when you were not sure where you were and what you were doing?" He urged distinguishing true positive answers from seizures or alcoholic blackouts.

I believe it is important that psychiatrists also be aware of a legal requirement in many jurisdictions to report such episodes to public health authorities. California's requirement is most stringent; most other jurisdictions invite the physician to report if it is deemed appropriate. The California Health and Safety Code, Section 410, states,

> Any person age 14 years or older who during the preceding three years has experienced on one or more occasions a lapse of consciousness or episode of marked confusion caused by any condition which may bring about lapses, including momentary lapses of consciousness or episodes of marked confusion, and which may become chronic, shall be considered to have a disorder characterized by lapses of consciousness and shall be reportable.
>
> This includes persons subject to lapses of consciousness or episodes of marked confusion resulting from neurological disorders, diabetes, cardiovascular disease, alcoholism or excessive use of alcohol sufficient to bring about blackouts (retrograde amnesia for their activities while drinking), senility, or any other condition which may cause lapses of consciousness or marked confusion and which may become chronic.

Such information is not protected by canons of confidentiality. The judicial counsel of the American Medical Association has held, "The physician should not reveal confidential communications or information without the expressed consent of the patient, *unless required to do so by law.*" California law explicitly requires any physician having knowledge of such episodes to report them under penalty of the doctor's own liability. Thus, when asking important clinical questions, the psychiatrist must be aware of personal legal responsibility and liability.

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Double Depression and Somatization

SIR: Daniel N. Klein, Ph.D., and associates (1) have emphasized the strong evidence for the clinical significance of double depression. Clinicians frequently encounter patients with major depression who also suffer from dysthymic disorders (2). We are currently carrying out a comprehensive prospective study of double depression. During the course of this study we have made some interesting observations. There were patients with major depression who reported predominantly somatic symptoms (mainly pain) that were exacerbated for a period of a few months and who met the criteria for major depression with melancholia. The somatic symptoms were worse in the morning. These patients reported self-blame, feelings of guilt, and early-morning awakening during this period. On the Newcastle scale, these episodes met the criteria for endogenous depression. After the severe episode subsided, the patients reported mild, persistent somatic symptoms without features of endogenous depression and met the criteria for minor depressive disorder.

In our sample of 32 patients with double depression, there were five who presented with somatization rather than sadness of mood. However, lack of interest in surroundings and general activities was found to be a prominent feature. Criterion A for the diagnosis of major depression in *DSM-III-R* requires either sadness of mood or diminished interest or pleasure. The patients in these five cases had a marked lack of interest in general activities, along with somatic symptoms, and thus met the criteria for major depression.

We consider that these are cases of masked double depression or somatized double depression (3). Somatic symptoms are a common presenting feature in major as well as minor depression (4), masked or unmasked (5), in our culture, but this somatization or masking of double depression was rather unexpected. Because of the physical presentation and exacerbation of physical symptoms during major depression, these patients had consulted nonpsychiatrist physicians primarily. Some of our patients had had at least two or three previous episodes of somatization with features of endogenous depression.

We submit this report to draw the attention of *Journal* readers to this interesting presentation of double depression.

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Photophobia in Depression

SIR: We were interested by the report of Hector Gerbaldo, M.D., Ph.D. (1) on depression and photophobic behavior because we have seen a similar symptom of photophobia in a depressed obsessional man who has been poorly responsive to treatment. The light-avoidance rather than light-seeking behavior probably has little to do with the melanotonin-mediated mechanisms setting circadian rhythms and influencing mood.

Mr. A, a 30-year-old man, had a major depressive episode with numerous somatic preoccupations and pain in his eyes, which forced him to wear sunglasses. The amount of light that bothered him varied, but he would often demand that the blinds be drawn even on cloudy days. While there was no blurring or difficulty focusing, he had the sensation of "wearing the wrong pair of glasses" and was unable to read. Several antidepressants were tried, and the best regimen was phenelzine plus clonazepam. However, the patient resumed taking maprotiline because of sleep disturbance when he took the monoamine oxidase inhibitor. He continued to be fixated on his eye discomfort and had some residual anxiety (with muscle spasms).

Ophthalmologic consultation showed visual acuity of 20/15, equal pupils, normal fields, fundi, and ocular excursions, and orthophoria in the cardinal positions. The patient's Farnsworth-Munsell 100 Hue Test responses and visual potentials were normal or above average. The ERG intensity series demonstrated normal B/A wave and B wave implicit times, but there was a one-standard-deviation deficit in B wave amplitude and a two-standard-deviation deficit in the amplitude of response to flicker at 30 Hz, neither of which was considered significant.

The patient was seen as suffering from depression with somatic symptoms (somatoform pain disorder, hypochondriasis), his severe anxiety and obsessional personality traits contributing to their emergence.

The mechanisms, relationship with anxiety and depression, and etiologic factors in somatization have been well outlined by Lipowski (2). Ocular symptoms (inability to read print without severe pain, inability to drive, avoiding sunlight, and the need to rest the eyes after brief tasks) with or without headaches may be present as conversion disorder (3).

Excessive light sensitivity is an unusual sequela of brain disease occurring in trigeminal neuralgia, migraine, meningitis, subarachnoid hemorrhage, sellar and suprasellar tumors, and retrobulbar neuritis, and after trauma (4). True photophobia (pain on exposure to light) is usually associated with inflammatory conditions of the cornea, conjunctiva, iris, or ciliary bodies because of their rich pain-sensitive innervation (3). Dazzle (painless exaggeration of brightness) may occur in certain ocular disorders or on a central basis due to a thalamic lesion (5).

Anxiety may lead to an increase in sympathetic tone, producing relatively large, equal-size pupils that show a bilaterally sluggish reaction to light, with normalization on later examination (Bumke's pupils) (3). In Adie's syndrome, a disorder of pupillary sphincter function due to postganglionic denervation, the patient demonstrates supersensitivity to cholinergic agents; the lack of response to light causes problems with glare, especially from fluorescent light, and with near tasks (3). Spasm of the near reaction, most often associated with stress, may cause blurring of vision. One case of intermittent pupillary sphincter and ciliary muscle spasm due to parasympathetic hyperactivity has been reported (6). It is possible that some of the visual disturbances found in psychiatric disorders may be attributed to sympathetic and/or parasympathetic dysfunction without invoking mechanisms affecting the circadian rhythms.

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Therapist-Patient Sexual Involvement

SIR: I want to commend Thomas G. Gutheil, M.D., for his lucid article on sexual relations between therapist and patient (1), which could have been as justly subtitled "Clinical Pitfalls" as "Medicolegal Pitfalls." My experience as a member of the APA Ethics Committee supports the idea that the majority of complaints about sexual involvement come from patients with borderline personality disorder or traits and mostly concern therapists who are unskilled in treating such patients or who disregard their more usual ways of practice. While nothing, except perhaps the threat of a lawsuit or loss of license, will deter the consciously abusive therapist (who often is also a repeat offender), education is the best preventive for most practitioners. Dr. Gutheil clearly pointed out the kind of patients, and patient wishes, that tend to elicit boundary violations and the warning signals in patients and in themselves that therapists need to heed. Furthermore, he vividly showed that well-meaning approaches without the proper education (and perhaps supervised treatment experience) can easily lead to treatment disasters for both patients and therapists.

It is to Dr. Gutheil's credit that he wrote this article in an era where any attempt to deal with the abused patient's behavior or dynamics is generally avoided for fear that the therapist will be seen as "blaming the victim." His article makes clear that we as psychiatrists have a professional obligation to know how to recognize and how to treat these patients in order to prevent their victimization by us.

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KATHLEEN M. MOGUL, M.D.
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Comorbidity Versus Misdiagnosis of Axis II and Axis III Disorders

SIR: Elizabeth M. Schmid, M.D., and associates presented a case report (1) which raised several important questions: What constitutes misdiagnosis of an axis II disorder? What establishes the presence of a seizure disorder? And when is labeling not labeling?

Borderline personality disorder is likely to be a disorder with multiple contributing factors, both biological and experiential (2). We have been strong proponents of the view that axis I and axis III disorders play an important and often overlooked role in borderline personality disorder (3), but we believe that the concept of comorbidity is more appropriate than the concept of misdiagnosis in most cases. Suggesting that the presence of an axis III diagnosis such as a seizure disorder invalidates an axis II diagnosis of borderline personality disorder may cloud rather than clarify the diagnostic and etiologic issues.

Instead, the presence of a seizure disorder should raise the question of how a seizure disorder contributes to the observed symptoms captured by the descriptive diagnosis borderline personality disorder. In our experience, effective treatment of an established seizure disorder relieves many of the more dramatic symptoms of borderline personality disorder but does not fundamentally alter the typical styles of ego defense and cognition. It would therefore be interesting to know whether during carbamazepine treatment the patient described by Dr. Schmid and associates continued to show any of the interpersonal and cognitive traits usually associated with borderline personality disorder.

In assessing the case for misdiagnosis, it is also important to recognize that seizure disorders are often difficult to establish or exclude. Clinical presentation is vital, but hardly leads to error-free diagnosis; dissociative disorders, for example, may present with similar symptoms. The significance of brain electrical activity mapping (BEAM) abnormalities such as those reported by Dr. Schmid and colleagues is controversial. Response to an anticonvulsant such as carbamazepine is consistent with a seizure disorder, but it neither proves the presence of a seizure disorder nor invalidates the original diagnosis of borderline personality disorder, since patients with borderline personality disorder (and other nonepileptic psychiatric disorders) may experience noteworthy benefits from carbamazepine in the absence of a seizure disorder or EEG abnormalities (4, 5).

The possible advantage of relabeling this patient's disorder as seizure disorder is clear; it led to apparently effective treatment with carbamazepine. However, the label "seizure disorder" may itself have important consequences, and the use of carbamazepine might also have been arrived at through a careful review of this patient's symptoms and the existing research on borderline personality disorder. The advantage of labeling the borderline personality disorder diagnosis as a misdiagnosis is less apparent and seems to imply that the borderline personality disorder diagnosis should be used only when no other diagnosis can be applied. We believe this approach may inhibit research into the origins of borderline personality disorder and may enhance rather than diminish whatever perjorative connotations the term "borderline personality disorder" conveys.

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DAVID L. GARDNER, M.D.
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Effects of Lithium on Thyroid Function

SIR: I read with interest the comment of Mogens Schou, M.D. (1) on lithium's effect on the thyroid and agree that patients respond well to supplementary thyroxine treatment. I also agree that lithium-induced hypothyroidism is not a particular problem in the first 6 years of lithium therapy unless the laboratory work-up reveals an exaggerated response to a thyrotropin-releasing hormone/thyrotropin (TSH) test and/or a positive antithyroid antibody screen (2, 3). However, lithium-induced grade 1 or grade 2 hypothyroidism could be a more important problem for patients treated continuously for 6 or more years. In one study with a comparatively small sample (3), three of 10 patients treated continuously with lithium for 5 or more years subsequently experienced thyroid failure but were then treated successfully with levothyroxine. An additional patient in this group of 10 had persistent mildly elevated levels of TSH for more than 2 years and is perhaps a potential candidate for hypothyroidism in the future, as this development was seen in the other patients with thyroid failure. Accordingly, Dr. Schou's statement that "hypothyroidism occurred with an incidence of 2 per 100 years of lithium exposure" could be misinterpreted.

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Neurobiology of Panic Disorder

SIR: The model proposed by Jack M. Gorman, M.D., and associates (1) to help describe panic disorder was very thought provoking. The authors presented a hypothesis that attempts to integrate three separate neuroanatomical areas (the limbic system, the prefrontal cortex, and the brainstem) into the continuum of the disease state. While the hypothesis has strong merit on its own, it is particularly fascinating in conjunction with recent findings that appear to implicate cholecystokinin in the etiology of panic attacks.

Intravenous administration of cholecystokinin-tetrapeptide can induce panic attacks in healthy volunteers as well as in patients with panic disorder (unpublished manuscript of J. Bradwejn et al., 1988). An enhanced sensitivity to the panicogenic effect of cholecystokinin-tetrapeptide has also been demonstrated in these patients (2). The finding that cholecystokinin can modulate a disorder that presumably has a significant limbic component is, perhaps, not surprising. Cholecystokinin is present, to a large degree, in the hippocampus and the related structures of the limbic system, including the entorhinal and cingulate cortical areas as well as the septum. Further, although various neuropeptides exist in measurable quantities in the neocortex, cholecystokinin appears to be one of the most prevalent. There is also evidence that cholecystokinin mesolimbic and mesocortical pathways project from the ventral tegmental area to the basal forebrain and ventral prefrontal cortical areas. Other studies have shown that there appear to be afferent cholecystokinin-containing projections that originate in the brainstem and terminate in discrete cortical regions and that there may be cholecystokinin-positive interneurons in the dorsal raphe (3). Further, Hokfelt et al. (4) have shown that there are several cholecystokinin-immunoreactive cell bodies located in the dorsal strip of the nucleus tractus solitarii and in the area postrema. These neurons—at least those located in the dorsal strip—probably also contain norepinephrine (4) and may therefore be further implicated in the adrenergic components of panic attacks. Cholecystokinin also exerts a powerful excitatory action on limbic neurons that can be antagonized by benzodiazepine receptor agonists (5).

The body of evidence which suggests that cholecystokinin-mediated mechanisms are at work in panic disorder is all the more persuasive when it is viewed concurrently with the structure delineated by this new "neuroanatomical" hypothesis. Future research may determine that a more accurate model incorporates elements of both systems. It would be interesting to see the results of experiments designed to elucidate the effects of cholecystokinin agonism in relation to the various prefrontal, limbic, hippocampal, and brainstem structures. Such studies might include in vivo positron emission tomography imaging of cholecystokinin in, for example, patients with panic disorder and in volunteers. Clinical research should also be undertaken to explore potential differential action between cholecystokinin antagonism and conventional treatment of anticipatory anxiety and panic attacks.

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Exercise and Anxiety Disorders

SIR: Although in their comprehensive effort to integrate biological and behavioral perspectives on panic disorder, Jack M. Gorman, M.D., and associates (1) noted only that "exercise stress tests do not cause panic attacks," clinicians clearly identified the exercise intolerance and poor cardiovascular fitness of anxious patients in the first half of this century, and the importance of this association was directly reflected in the diagnostic terms of that time, including "neurocirculatory asthenia," "irritable heart," "effort syndrome," etc. And, as Pitts and McClure (2) reported, exercise testing in the laboratory has confirmed this clinical impression. Patients were "unable to perform as much work as normal controls," and "the characteristic anxiety symptoms were often evoked by the exercise and appeared to be concomitant with the extremely rapid rise of blood lactic acid." These exercise data were, in fact, what led Pitts and McClure to discover lactate infusion as a laboratory model for anxiety. Recently, Gaffney et al. (3) again demonstrated, using standard exercise testing, that panic disorder patients have "significantly lower cardiovascular fitness" than control subjects.

How might such exercise avoidance and lack of fitness emerge? One possible explanation is that anxious patients may "inherit brainstem loci that are hyperexcitable" (1) and may be biologically predisposed to a dysphoric interpretation of the sympathetic arousal associated with exercise. Alternatively, patients' early experiences of physical exercise may have been in contexts of negative emotional valence, such as being clumsy at summer camp or frightened by rough treatment in a swimming pool. Others, reared by anxious, exercise-avoidant parents, may grow up unfit, without the repeatedly reinforced positive association of pleasurable regular exercise and adrenergic arousal.

Through some combination of such biological and behavioral factors anxious individuals may only perceive adrenergic arousal as dysphoric, dangerous, frightening, and to be avoided. Once established, this emotionally negative association to exercise may in turn be generalized to other challenging or stressful situations that are accompanied by sympathetic discharge.

As Hales and Travis (4) and others have suggested, supervised exercise programs should be investigated as a major therapy (either singly or in combination with other modalities) for panic disorder and other anxiety syndromes. Exercise programs can be used for those individuals who, though frightened, are interested in increasing their comfort with and capacity for exercise. Patients choose the type of exercise that appeals to them (jogging, swimming, etc.) and whether to receive individual or group treatment. Sessions begin well below the patient's initial exercise capacity because of the biologically inherent and/or behaviorally acquired dysphoria triggered by sympathetic discharge. The pace and duration of the exercise are increased very gradually as patients are desensitized to, and become familiar and comfortable with, the physical sensations of adrenergic arousal in a positive emotional context. Anticipatory anxiety, and possibly panic attacks as well, may be reduced. Patients can then be helped to generalize this learning to other avoided everyday situations, which can then be freed from their associated crippling terror. The role of exercise-induced endorphin release (5) and changes in other neurohumoral functions may also be important in this learning process. As an added benefit, exercise will certainly enhance fitness and may improve health and longevity (6).

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Verifying Patients' Reports of Childhood Abuse

SIR: I am concerned about the title of the paper "Childhood Trauma in Borderline Personality Disorder" by Judith Lewis Herman, M.D., and associates (1). I write this letter with grave trepidation that it will be misconstrued. I have no doubt that child abuse is a serious public health problem. Certainly, the authors were also entitled to make arbitrary judgments about how they scored events as "culturally-accepted" or "equivocal" in their study. My concern is the apparent lack of verification that the events in question even occurred. It doesn't take much clinical experience to realize that histories obtained from patients and informants often vary markedly. It may be argued that there was no reason to doubt the subjects, but no court would uphold such unsubstantiated claims. Regardless of the controversial implied conclusion that there were cause-effect relationships in this matter, I think science, clinicians, and the public will be better served if the titles (and texts) of such reports clearly reflect that the abuse was "reported" with or without collateral substantiation.

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Dr. Herman and Associates Reply

SIR: The problem of credibility in trauma-related syndromes has been with us for at least a century. In "The Aetiology of Hysteria" (1), published in 1896, Freud first proposed a link between the archetypal psychological disorder of women and a history of early sexual abuse. This classic paper addressed the issues of credibility and doubt more thoroughly and eloquently than we could ever hope to do. Within a year, however, Freud repudiated his "seduction theory." This reversal was not based on clinical evidence from patients or other informants, but rather on Freud's *unwillingness to believe* that sexual abuse of children could be as common as it is now known to be (2). Freud went on to develop a psychology that emphasized the importance of drives, wishes, and fantasies while minimizing the importance of real-life events. The legacy of this tradition is an expectation that people distort or exaggerate their experiences of childhood abuse.

Contemporary clinical work with incest survivors addresses the credibility problem directly. Since survivors often doubt their own recall, an important part of their recovery is taking active steps to validate their memories. In a recent study of 53 women in group treatment (3), 39 (74%) were indeed able to obtain independent corroboration of their abuse histories, either by direct admission of the perpetrator, by testimony of another victim or witness, or by physical evidence such as pornographic photographs. Another 9% obtained highly suggestive supporting evidence. Only 6% were unable to obtain any confirmation in spite of active attempts to do so. The remaining 11% made no attempt to validate their memories. The findings in this study accord with those of several other careful forensic investigations. The figure for unsubstantiated complaints seems to hover around 5% (4). This same figure might apply to the subjects in our study of childhood trauma in borderline personality disorder. However, the observational design of our study operated to minimize the likelihood of false reports of childhood abuse, since such reports did not result in any social consequence or interpersonal reward.

The larger question raised by Dr. Rich's letter, however, has to do with the wish for certainty in a scientific article. Although the limitations of retrospective histories are generally recognized, corroborating evidence is not usually considered necessary. There seems to be something special about data on childhood abuse that demands this extraordinary standard of proof. We suspect, in fact, that no amount of evidence, clinical or legal, will every finally put the credibility question to rest. Denial is a phenomenon of social as well as individual psychology, and we as professionals are not immune to it. No one wants to believe in the reality of the horrors perpetrated against children.

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Tricyclic Antidepressants and Malignant Hyperthermia

SIR: In a recent letter to the Editor of this journal, Roger C. Burket, M.D., and Jon D. Hodgin, M.D., reported using fluoxetine to treat depression in a patient susceptible to malignant hyperthermia (1). Because of the patient's biopsy-proven susceptibility to malignant hyperthermia and a family history of lethal malignant hyperthermia, they regarded the use of traditional antidepressants as a severe risk. Drs. Burket and Hodgin also stated that malignant hyperthermia has been associated with use of monoamine oxidase inhibitors (MAOIs) and haloperidol. Their caution was unwarranted, and they seem to have blurred the distinction between true malignant hyperthermia and other drug-induced hyperthermic reactions. Antidepressants rarely cause hyperthermic reactions, but there is no evidence that susceptibility to malignant hyperthermia correlates with such reactions (2).

Malignant hyperthermia is precipitated most often by inhaled anesthetics such as halothane in combination with succinylcholine. MAOIs have been associated with hyperthermia in overdose or in adverse interaction with other drugs. Neuroleptics, of course, may cause neuroleptic malignant syndrome, which symptomatically closely resembles malignant hyperthermia (3), but there are no reported cases of neuroleptic malignant syndrome or other severe hyperthermic reactions among patients susceptible to malignant hyperthermia who have been treated with neuroleptics, tricyclic antidepressants, or MAOIs (2). It would be prudent to be careful in the use of psychotropic medication for a patient with a history of a previous, poorly defined, severe hyperthermic reaction to medication. However, when it is known that the patient has true susceptibility to malignant hyperthermia, there is no need to withhold tricyclic antidepressants or other psychotropic agents.

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Drs. Burket and Hodgin Reply

SIR: In response to Dr. Levenson's excellent points we wish to offer the following. The main issue in the case we presented is whether a particular psychoactive agent may facilitate a malignant hyperthermic episode in a susceptible patient, not the confusion between malignant hyperthermia and other hyperpyrexic reactions. Dibenzazepine antidepressants have been implicated in aggravating malignant hyperthermic reactions (1). However, like Richter and Joffe (2), we are not currently aware of clearly documented case reports of tricyclics as precipitants of malignant hyperthermia. In fact, those authors reported a case in which three tricyclic antidepressants were safely used sequentially in a patient with proven susceptibility to malignant hyperthermia. On the other hand, as we are all aware, malignant hyperthermia, when it occurs, has significant morbidity and potentially lethal consequences for the patient, even with current treatment modalities (3).

As Mulrooney (4) recently stated, "Where there is doubt concerning the triggering potential of a particular drug a 'worst case' approach should be taken." With this thought in mind, we feel that the use of a tricyclic antidepressant in a youthful patient with biopsy-proven susceptibility to malignant hyperthermia should be approached with extreme caution and that the documentation of the safe use of fluoxetine in a depressed adolescent in these special circumstances is a worthwhile addition to the literature.

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Ergotism in Lethal Catatonia

SIR: The article by Edgar Castillo, M.D., and associates on the "Clinical Differentiation Between Lethal Catatonia and Neuroleptic Malignant Syndrome" (1) distinguished between the two syndromes so as to recommend divergent treatment plans. The authors disagreed with earlier assumptions that neuroleptic malignant syndrome and lethal catatonia share a common pathophysiological origin. A reexamination of one possible cause of lethal catatonia, namely chronic ergotism, a condition associated with dopaminergic overload, may further substantiate their contentions.

The catatonia, agitation, and delusions of the patient with lethal catatonia described by the authors are consistent with, but not pathognomonic of, ergotism. However, when considered in conjunction with the coexisting physical signs of skin discoloration and acrocyanosis—hallmarks of the peripheral vasocclusion of ergotism—as well as tense muscles and cramped posture, the psychiatric presentation is highly suggestive of this multisystemic mycotoxicosis (2–5). The 10%–30% mortality rate (2, 5) of neurogenic ergotism approximates the outcome of neuroleptic malignant syndrome and catatonia.

Epidemiological data support the possibility that the case described by Dr. Castillo and associates, excerpted from a German-language publication of 1934, represented a case of ergotism. Major European outbreaks of bread poisoning, spread by the ergot-elaborating rye, grain, and grass fungus *Claviceps*, recurred sporadically until 1927. In that year, 7,000 Ukrainians, plus Manchester's rye-bread-eating Jewish immigrants of Russian-Polish descent, were afflicted (2). Because ergotism was acquired through a social practice shared by household members, it was overrepresented among relatives, further mimicking inheritable functional disorders. In the case described by Dr. Castillo and associates, the patient's sister had also succumbed to lethal catatonia. When seen today, ergotism is almost exclusively iatrogenic, most often secondary to use of ergotamine. It is also reported to follow administration of bromocriptine and heparin diergotrate. Although the literature contains no specific references to ergotism induced by the many ergot-derived recreational hallucinogens, this source may be worth bearing in mind. Psychiatric manifestations that occur early in the clinical course of ergotism commonly go undiagnosed. Eventually, death, cerebral vascular accidents, myocardial infarction, or peripheral ischemia necessitating amputation may intervene. As a result, such cases are more often reported in legal proceedings than in the psychiatric or medical literature.

Because ergot is a central medullary stimulant with potent dopaminergic, serotonergic, and adrenergic agonist properties, its effects contrast with the dopamine blockade of neuroleptics. These central effects occur independent of, and at lower doses than, the peripheral α-adrenergic blockade responsible for peripheral ischemia. Curiously, bromocriptine, a dopamine agonist recommended in the treatment of neuroleptic malignant syndrome, is also an ergot and thus is capable of inducing ergotism. The use of this dopaminergic ergot in the treatment of ergot-induced catatonia would be just as contraindicated as neuroleptics are in the treatment of neuroleptic malignant syndrome.

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SHARON PACKER, M.D.
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Dr. Rubin Replies

SIR: Dr. Packer's interesting hypothesis that some early cases of lethal catatonia might have been unrecognized cases of ergot poisoning certainly deserves additional historical study of the individual case reports and the environmental circumstances surrounding the occurrence of these incidents.

ROBERT T. RUBIN, M.D., PH.D.
Torrance, Calif.

Derealization Without Depersonalization

SIR: I have to disagree with the description of depersonalization and the correctness of this diagnosis as presented by Eric Hollander, M.D., and associates in their letter to the Editor "Pharmacological Dissection of Panic and Depersonalization" (1). Using the patient's own very good and unbiased description of her feelings, the authors overlooked the existence of an almost textbook example of derealization without depersonalization, which belongs under atypical dissociative disorder (diagnosis 300.15) in *DSM-III*. The patient described her condition and feelings very clearly and very exactly. She said, "Everything feels unreal, things seem out of place and too close, there is a fogginess like a veil is over everything, I feel nauseated, and I feel separate from my friends." In other words, external things (i.e., not the patient's self) and her surroundings felt unreal, hence the term "derealization." Feelings of nausea basically have nothing in common with depersonalization. The feeling of being separate from friends does not *eo ipso* indicate change of the reality of one's own self.

The term "depersonalization" was suggested by Laurent Dugas on the basis of Krishaber's observations, as noted by Nemiah (2), who commented,

> Some clinicians . . . distinguish between depersonalization and derealization. They apply depersonalization to the feeling that one's body or one's personal self is strange and unreal; they apply "derealization" to the experience of perceiving objects in the external world as having the same quality of unreality and estrangement. Strictly speaking, that distinction provides a more accurate description of the phenomena than does lumping them all together under the category of depersonalization. Indeed, if a single term is to be used, derealization is the more appropriate, since it refers to a characteristic change in the perception of objects common to all of them—to self, body, or external world—whereas depersonalization is more limited in scope. (p. 1556)

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GEORGE O. KRIZEK, M.D.
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Dr. Hollander and Associates Reply

SIR: We thank Dr. Krizek for his interest in and close reading of our letter. We agree with him that the patient described in that letter suffered predominantly from derealization. However, she experienced feelings of perceptual alteration toward both herself and objects in the environment, and according to *DSM-III-R* she would meet criteria for depersonalization disorder. *DSM-III-R* states that derealization is frequently present in depersonalization disorder.

Furthermore, we are not sure whether the distinction between depersonalization and derealization is really a valid and helpful one. In our experience, most patients with depersonalization also suffer from derealization, and vice versa. Depersonalization and derealization symptoms respond to similar types and dosages of medication, and following effective treatment, both resolve in a similar time course. In fact, there is emphatically no evidence for pharmacological dissection of depersonalization and derealization. Since the two syndromes usually occur together and have similar treatment response, perhaps they share a common underlying pathophysiology. Nevertheless, there is a dearth of studies to date on similarities and differences between depersonalization and derealization, and this clearly deserves more attention.

ERIC HOLLANDER, M.D.
JANET FAIRBANKS, M.D.
CONCETTA DECARIA, M.S.
MICHAEL R. LIEBOWITZ, M.D.
New York, N.Y.

Franz Kallmann's Views on Eugenics

SIR: The thoughtful review by Elliot S. Gershon, M.D., of Müller-Hill's book on the nefarious eugenics movement in Nazi Germany (1) prompted me to write to the reviewer about the references to Franz Kallmann. Indeed, the statement quoted from Kallmann's 1935 talk in Germany (after which he was not allowed to speak or publish again) appears to advocate sterilization of relatives of schizophrenic patients on eugenic grounds, and although it carried no explicit reference to compulsion, this inference might be made because of the laws of that time (not only in Germany).

In his first writing on the subject in this country after he was forced to leave Germany, Kallmann (2) said of certain marriages, "The danger of the development of new schizophrenic cases, arising from such unions, is so great that there should be legal power to intervene, in addition to the general eugenic program of the biological education of all adolescents, marriage counsel, obligatory health certificates for all couples applying for a marriage license, and the employment of birth control measures." A year later he wrote, "In democratic countries with high standards of ethics and moral discipline, the general public should be educated rather than forced to realize the advisability of submitting to reasonable eugenic measures adopted for the perpetuation of common happiness and security" (3). Thereafter, his emphasis was increasingly on family mental health and responsible parenthood, and all of those who knew him, here and abroad, always considered him beyond reproach as a geneticist, psychiatrist, and humanitarian counselor.

It would be unfortunate, therefore, if the reviewer's accurate statement that "Kallmann later became an important founder of psychiatric genetics and human genetics in the United States" (1) were to be used to taint the increasingly productive research efforts in these fields today, which promise to offer definitive means for prevention and treatment of disease.

Dr. Gershon replied to my letter, referring to his earlier appreciation of Kallmann (4) and giving me permission to quote from his letter. What he meant to imply in mentioning Kallmann specifically, he wrote, was that "even respected psychiatric geneticists, who could in no way be accused of Nazism, would advocate sterilization on eugenic grounds" because of "how accepted and unremarkable the eugenic outlook and advocacy of sterilization was at the time." Dr. Gershon considered that "at the time of the 1935 lecture, [Kallmann] had taken on certain morally indefensible positions of his time and surroundings . . . [including] compulsory sterilization of people who would not consent to it, but of course never . . . racism or euthanasia."

In his letter, Dr. Gershon added that "on balance Kallmann's scientific life is one of courageous defense of a field, psychiatric and human genetics, which helped it survive" and that Gershon did not "wish to support anyone who would apply the taint of racism to Kallmann, or to psychiatric genetics in its current incarnation . . . . If this is implied in the book review, it is to be regretted."

I suppose it would require a clairvoyant investigative reporter to distill the absolute truth about Kallmann in the 1930s, and unfortunately neither he nor his widow is alive to be interviewed. However, I knew him well from 1952 until his death in 1965, knew many of his contemporaries, wrote about his work (5), and with many colleagues today can credit him with the foresight that promises now to yield so rich a harvest of useful scientific knowledge.

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JOHN D. RAINER, M.D.
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Sensitivity to Gravitational Changes

SIR: I was intrigued by the letter to the Editor from Daniel Traub-Werner, M.D. (1) in which he postulated that people with agoraphobia with panic attacks may be highly sensitive to gravitational changes. Could this not also explain the high degree of discomfort these people experience in elevators?

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JANET M. BERG, M.D.
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What Women Want

SIR: The letters to the Editor from Lynn Whisnant Reiser, M.D. (1) and William G. Niederland, M.D. (2) concerning Sigmund Freud's famous (infamous?) question "What does woman want?" has stimulated me to present my viewpoint on the matter and to go one step further and attempt to answer the question. Both Dr. Reiser and Dr. Niederland lean in the direction that I have always felt was correct; that is, Freud spoke the words in humor. It has always been my suspicion that Freud asked the question with tongue in cheek, much as I suspect that Shakespeare wrote *Romeo and Juliet* as a comedy, only to find to his amazement that people take these things seriously and react to them as if they were high drama. Freud knew what women want because he listened to them in depth as patients and also because he had excellent female analysts from whom he learned (Helene Deutsch, Jeane Lampl-de Groot, Marie Bonaparte, and, of course, Anna Freud). Freud knew that there are genetic, hormonal, anatomical, and psychological differences between the sexes. He also knew that there is a great deal of similarity. Neither the differences nor the similarities have anything whatsoever to do with superiority or inferiority. Unfortunately, the question of superiority or inferiority commonly inserts itself as the latent content whenever the manifest content of similarities and differences arises. This only confuses the issue.

Explaining what Freud really knew about the psychodynamics of women by the end of his career would take too long and would fill books itself (all 24 volumes). The following anecdote will serve to illustrate the answer to the famous question. Marilyn Monroe, at the height of her successful career, was at an emotional low and in a state of despair. In frustration at this seemingly contradictory position, a friend asked her, "What is it you really want?" Ms. Monroe, without hesitation, replied, "What I want is—everything." So here it is, the famous answer to the famous question "What do women really want?" "Everything." Of course, one should also remember that all men want the exact same thing.

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JAMES L. KNOLL III, M.D.
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Reprints of letters to the Editor are not available.

Annual Reports to the Membership

The following are edited versions of the annual reports by the APA Secretary, Treasurer, Medical Director, Speaker, and Speaker-Elect and the chairpersons of the APA Committee on Constitution and By-Laws, Committee on Membership, and Committee of Tellers, which were given at the annual business meeting in San Francisco on May 8, 1989. The annual report of the American Board of Psychiatry and Neurology, Inc., appeared in the August issue of the Journal.

Report of the Secretary: Summary of Actions of the Board of Trustees, May 1988–May 1989

Elissa Benedek, M.D.

OVERVIEW

It is my personal and Constitutional privilege as Secretary to report to the membership the actions taken by the Board of Trustees and the significant activities of the Association over the past year. The actions reported do not include a number of issues referred to appropriate components for further study and recommendation. As required by our Constitution, especially important issues will be discussed and clarified at the annual business meeting, and a full report will be published in the *American Journal of Psychiatry.*

Membership

As of Jan. 1, 1989, the membership was 35,168, which represents a net gain of 862 members during 1988. Members-in-Training and Medical Student members (N=6,252) constitute 18% of the total membership. Involvement of residents in the activities and components of the Association continued to increase. A voting Member-in-Training Trustee and nonvoting Member-in-Training Trustee-Elect began to serve on the Board of Trustees in May 1988; an ad hoc committee revised the procedures for nominating the candidates for the position of Member-in-Training Trustee-Elect, and the Board approved them in March 1989. The Committee of Residents and the resident fellowship programs continue to have representation on the Board. The Assembly continues to have a Member-in-Training representative and deputy representative on each of the seven area councils. In conjunction with the American Medical Association (AMA) Section Council on Psychiatry, APA created a component of young psychiatrists (those who have completed their residencies within the past 5 years or who are under 40 years of age). In addition, APA has a young physician delegate and alternate delegate in the AMA House of Delegates.

Member Benefits

During 1988, the Committee on Special Benefit Programs proposed, the Assembly endorsed, and the Board authorized implementation of a pilot project that will provide financial planning services to members in two district branches. The project is offered through Grande Financial Services, Inc., a subsidiary of Raymond James Financial, Inc., and will be monitored by the Committee on Special Benefits. The program offers professional advice to individual subscribers on a wide variety of planning services, including cash flow, income tax analysis, insurance, education, investments, retirement, and estate tax.

The Legal Consultation Plan, offered by the Committee on Special Benefits, continues to be well subscribed and successful. The committee also offers seminars on tax reduction strategies and risk management methods. In December 1988, the Board authorized the committee to develop a seminar for residents on career choices in psychiatry.

With respect to the APA insurance programs, the Board took a number of actions throughout 1988 to consolidate the oversight and monitoring functions within the APA component structure. The Board Committee on Insurance is now responsible for oversight of both the professional liability and the life, accident, and health insurance programs. In September 1988, the Board transferred the Risk Management Subcommittee of the APA Insurance Trust and the Subcommittee on Member Life, Accident, and Health Insurance to the Board committee and authorized funding of the component activities and staffing by the APA Group Insurance Trust. The Assembly Executive Committee established a subcommittee on APA insurance programs to increase communication with the members about the programs. *Psychiatric News* now features a column called "Benefact," which provides information and addresses concerns about the APA insurance programs. In addition, APA has provided an ombudsperson to directly respond to inquiries and concerns.

In general, the APA group life, accident, and health insurance program has had a good year, but the APA major medical plan continues to suffer losses. For a second year, claims payments have exceeded premiums collected. The Board Committee on Insurance recommended a number of options to the Board in March, and the Board voted to temporarily modify the program to provide a lifetime maximum of $100,000 for inpatient psychiatric treatment, with the understanding that after further consultation a specific cap could be set by means of the Executive Action mechanism. As soon as the redesigned plan is ready it will be announced to the entire membership. The APA professional liability insurance program served more than 10,000 APA members in 1989. The May 1, 1989, renewal process went smoothly, after implementation of a number of suggested changes. The program continues to be comprehensive and competitive.

Ethics

The Association is revising "Procedures for Handling Complaints of Unethical Conduct" to comply with the Health Care Quality Improvement Act of 1986 and to provide accused members procedural rights during ethics investigations. The draft revised procedures have been reviewed by district branches and approved in principle by the Board and Assembly, and final approval by the Board is scheduled for June 1989. In addition, the Board and the Assembly approved adding the following statement to section 2, annotation 1, of *Principles of Medical Ethics With Annotations Especially Applicable to Psychiatry*: "Sexual involvement with one's former patients generally exploits emotions deriving from treatment and therefore almost always is unethical."

Judicial Affairs

APA has been involved in a number of judicial cases during the past year. Foremost is *CAPP v. Rank*, a California case concerning hospital admitting privileges for psychologists. APA has contributed financially to the California Psychiatric Association in support of this case since December 1986; however, with the current appeal by the California Association of Psychologist Providers (CAPP), the Board decided in September 1988 that APA should become an amicus in the California Supreme Court hearing of the case. In the summer of 1988, the California Court of Appeals issued a decision supporting the argument by psychiatry that psychiatrists have a broader range of experience and abilities, particularly with respect to the diagnosis of organic illnesses, and further, defined the scope of psychologists' licensing privileges as much narrower than that of psychiatrists'. The decision requires that before a psychologist can assume responsibility for a patient's treatment, the physician must rule out a medical basis for the patient's mental disorder and determine, on admission or thereafter, that the disorder is not subject to medical treatment. CAPP and its supporters requested a review by the California Supreme Court. This was granted, and APA, joined by the AMA and the American Association of Directors of Psychiatry Residency Training, filed a brief prepared by the Commission on Judicial Action in concert with legal counsel and a select group of APA members as consultants.

In December 1987, the Board authorized APA to file an amicus brief in the case *Charter v. The United States*, a right to refuse treatment case involving a prisoner in Butner, N.C. The U.S. Court of Appeals for the Fourth Circuit issued an opinion in September 1987 upholding a strong position for the patient's right to refuse treatment. The United States sought a rehearing, and since this was a federal appellate case and might set a precedent, the Commission on Judicial Action strongly recommended APA participation in the case. The case was reheard in June 1988 by the entire Fourth Circuit in Richmond, Va. The government ceded to APA, the major amicus on the government side, a third of its oral argument. I am happy to report that the decision strongly supported the position presented by APA, namely, that review of medication should exist at the institutional or professional level, not at the court level.

Government Affairs

The Joint Commission on Government Relations and the Division of Government Relations sponsor a state or federal legislative institute biennially. In March 1989, a successful Federal Legislative Institute was held in Washington, D.C., and members from 46 district branches attended. In addition to providing workbooks on federal legislative procedures and summaries of the 10 key legislative issues for psychiatry, the institute gave members the opportunity to hear presentations from key Congressional staff and legislators. The institute attendees visited Congressional offices, meeting with legislators and staff to discuss current issues of concern to psychiatry. During the Congressional reception, the first federal Jacob K. Javits Public Service Award was presented to Congressman Silvio Conte (R–Mass.) for his extensive efforts toward funding research on mental and addictive disorders.

The Board took a number of actions related to APA lobbying for the Kennedy-Waxman legislation on minimum health benefits. As originally introduced, this bill specifically excluded coverage for patients with mental disorders, but the bill was amended in the Senate Labor and Human Resources Committee to include a mental health benefit that was essentially comparable to most states' required psychotherapy benefits (i.e., 20 visits at 50% copayment) but did not affect self-insurance exemptions and had a limited impact on nondiscriminatory psychiatric medical management of patients and inpatient coverage under insurance plans covering small groups. The actions of the Board represent the discussion and concern within the Association about the various limitations of the bill and the potential impact on states that have higher levels of mandated coverage than provided by the bill. This legislation is slated for reintroduction in the 101st Congress.

I will briefly highlight three of the many successful lobbying activities APA conducted during the 100th Congress. First, we achieved bipartisan support within the House Ways and Means Committee, the House Energy and Commerce Committee, and the Senate Finance Committee of the first historic change in Medicare's psychiatric benefit in 22 years. In essence, the increase was a quadrupling of the psychotherapy benefit to $2,200 per year with a 50% patient copayment and the authorization of a nondiscriminatory medication management cap and an 80/20 copayment ratio. Second, under the Medicare provisions for catastrophic illness, exorbitant expenditures for patients with mental disorders in psychiatric units of general hospitals are now treated like expenditures for all other hospital care and outpatient prescription of psychopharmacological drugs. This was a victory for nondiscriminatory treatment of mental illness. Third, despite major budgetary deficits and cutbacks in many areas, APA succeeded in increasing funding for the research budget for the National Institute on Mental Health (NIMH), National Institute on Alcohol Abuse and Alcoholism, and National Institute on Drug Abuse, obtaining increases above inflation over the past 2 years. In both fiscal years the percentages of the increases exceeded those for the National Institutes of Health, and the increase for fiscal year 1989 was the highest ever obtained by NIMH.

The Corporation for the Advancement of Psychiatry Political Action Committee (CAP/PAC) was able to lend its support to 89 candidates running for seats in the U.S. House of Representatives and Senate; 89% won their election bids. CAP/PAC supported 19 candidates in Senate races, 84% of whom were winners. CAP/PAC directed early support to Senator Robert Kerrey (D–Neb.), Senator Richard Bryan (D–Nev.), Charles Robb (D–Va.), and James Jeffords (R–Vt.). Supported candidates were elected in 90% of the 70 House races to which CAP/PAC contributed. It is noteworthy that of all candidates supported, 13% were either challengers or running for open Congressional seats. Among CAP/PAC's House victories was the seat filled by psychiatrist James McDermott (D–Wash.). Dr. McDermott received early PAC support; his introduction to the Washington health community was led by CAP/PAC member Dr. Melvin Sabshin, who was his residency training director.

Public Affairs

In November 1988, the Joint Commission on Public Affairs and the Division of Public Affairs signed a formal agreement with the Upjohn Company through which the company will support APA production of three films about mental illnesses and psychiatric treatment for use by the district branches and by members in their community education efforts. This is a part of the 1988–1991 "Let's Talk About Mental Illness" campaign. The first film, "Panic Prison," is completed and premiered at the 1989 Public Affairs Network Institute held in San Diego in February.

During the National Public Affairs Institute, more than 180 participants from over 60 district branches were briefed on other materials prepared for the "Let's Talk About Mental Illness" campaign.

The institute provided opportunities for members to learn television interview and public speaking skills, to plan local public information campaigns, and to maintain good media relations. In addition, workshops provided advice on district branch newsletter production, including desktop publishing. Participants began preparations for Mental Illness Awareness Week, which will be the major annual public affairs activity in the "Let's Talk About Mental Illness" campaign. The campaign theme for the 1989 activities of the Joint Commission on Public Affairs and the Division of Public Affairs, including Mental Illness Awareness Week, is "Mental Illness: It's More Than What You Think." The 1988 Mental Illness Awareness Week was the most successful to date.

Other campaign activities supported in part by the Upjohn Company educational grants include a series of medical education workshops, public service announcements, and a program of symposia and exhibits that will travel to national meetings of other medical specialty societies. The Division of Public Affairs is also planning to combine the three films into a single program for possible public and commercial television syndication in 1990. APA has total control over the substance of all materials developed under the agreement.

Meanwhile, the Division of Public Affairs began a stepped up "Let's Talk to the Media About Mental Illness" effort, and requests from newspaper and magazine reporters and from television reporters and producers have increased about 30% over 1987–1988, with a significant increase in requests from national radio and television media. Increased media coverage, in turn, has stimulated demand for the "Let's Talk Facts About . . ." pamphlets, which are being printed and sold in bulk quantities by the American Psychiatric Press, Inc. The division mailed out over 60,000 pamphlets during the past year, thanks in part to promotion in *USA Today*, *Better Homes and Gardens*, *U.S. News & World Report*, and NBC Radio's "TalkNet."

AIDS

You will note a number of actions taken by the Board in 1988 related to the acquired immune deficiency syndrome (AIDS), including the establishment of a Commission on AIDS in September. The commission replaced two other components to provide a major focus for the Association in addressing issues and activities related to the epidemic of the human immunodeficiency virus (HIV). The commission reported to the Board in March 1989 on its current and future activities, including the following: 1) conducting a survey of the inclusion of information on AIDS in residency training programs, 2) developing better communication with district branches, including sharing information about HIV disease and AIDS-related activities on national and local levels, 3) preparing papers on neuropsychiatric aspects of AIDS, treatment refusal, prevention, risk-related behaviors, comorbidity, management issues (including depression and suicidality), conceptualization of the epidemic, policy issues, and the role of professional organizations, 4) cosponsoring the AMA AIDS conference on testing to be held in Montreal just before the International Conference on AIDS in June 1989, and 6) creating, in conjunction with the Division of Public Affairs, a "Let's Talk" pamphlet on AIDS.

During the 100th Congress, APA supported amendments introduced by Congresswoman Nancy Pelosi (D–Calif.) to provide counseling services for patients with AIDS. However, amendments protecting confidentiality of AIDS patient records were dropped in the final hours of negotiation.

Economic Affairs

The Association addressed many issues related to the changing patterns in the practice of psychiatry and emerging changes in the way service by psychiatrists is reimbursed. An invitational conference on managed care systems was held in November 1988 under the aegis of the Council on Psychiatric Services and the Task Force on Professional Practice Issues in Organized/Managed Care Settings; the conference proceedings will be published in the fall of 1989.

Commissioned by the Health Care Financing Administration and published in the fall of 1988, the report of the Harvard Resource-Based Relative Value Scale (RBRVS) study has the potential to be one of the more divisive issues currently facing the medical profession. The Board established a work group within the Council on Economic Affairs to prepare APA's analysis of the report's section on psychiatrists. In January 1989, selected members of the work group and our consultants met with staff of the Congressionally mandated Physician Payment Review Commission to discuss psychiatry's concerns with the coding in the AMA's *Current Procedural Terminology* (CPT) and problems with the RBRVS. The staff of the Physician Payment Review Commission were receptive to APA's concerns about coding and asked for APA input on proposed suggestions for coding. In addition, they asked for comments on the vignettes for psychiatry and why they were problematic. In a related development, NIMH published a request for a sole source contract for the "Refinement of the Development of a Resource-Based Relative Value Scale for Psychiatrist Services." This refinement would be conducted by Harvard University if the award is given, and one hopes that it would address the initially problematic areas. Harvard researchers feel it is important that the codes be amended before the refinement is actually completed. The results of the initial phase of the study were due at NIMH at the end of March. Working closely with the AMA, APA is accelerating its attempts to revise psychiatry's procedural codes in time for publication of *CPT-4* in 1990.

The Office of Economic Affairs has updated *The Coverage Catalog*, an extensive survey and analysis of coverage available for psychiatric services, and has produced several other publications concerning the economics of psychiatric practice. A Medicare specialist has been added to the staff of the Office of Economic Affairs to assist members in problems with Medicare. The office is preparing a marketing manual and offers technical assistance to district branches. In December 1988, the Committee on Financing and Marketing held a seminar on district branch marketing activities and concerns, and 15 district branches were represented.

DSM-IV

In May and June 1988, APA President Dr. Paul Fink appointed 16 individuals to the Task Force on DSM-IV. Since then, the 13 work groups, each with five or six members and 50–100 expert advisors, have begun the data and literature review that will precede any decisions on text and criteria. The chairpersons of all the work groups, other members of the task force, and a number of outside experts attended a 2-day methods and applications conference, at which they discussed in detail the ways in which reviews could be organized and could help to answer specific *DSM-IV* questions. The initial issues and discussions of all the work groups have been summarized in the semiannual "DSM-IV Update," which is circulated to interested individuals and groups within and outside APA (copies are available from the APA Office of Research).

Internal and External Liaison

Internal communication with the district branches and ways to strengthen and involve them more directly was a major topic at several meetings of the Board and the Assembly. A panel including the APA President (Dr. Paul Fink), the Speaker and Speaker-Elect of the Assembly (Drs. John McIntyre and Gerald Flamm), and a past president of the Ohio Psychiatric Association (Dr. Jerome Logan) discussed issues of interest and concern to district branches with over 100 district branch presidents-elect and staff in November 1988. Dr. Fink and other national leaders met with key local leaders during the 1988 annual meeting and again at the Institute on Hospital & Community Psychiatry.

An ad hoc committee of the Board continues to study APA's liaison activities, including their cost and benefits to APA. As authorized by the Board, the ad hoc committee is exploring how other psychiatry-based organizations can be more involved in APA's governance structure. Twenty APA liaisons to such organizations met during September to discuss existing and potential avenues for access to APA and to identify services APA could provide to some of these organizations. In addition, the Assembly Committee on Planning is addressing ways of involving representatives of psychiatry-based organizations within the Assembly.

APA supported the development of added qualifications in geriatric psychiatry by the American Board of Psychiatry and Neurology

(ABPN) and the American Board of Medical Specialties. The Ad Hoc Committee on Subspecialization has prepared a report proposing a definition of a subspecialty and criteria, procedures, and a governance structure for evaluating and processing requests for support within APA by groups seeking subspecialty status. The report will be widely reviewed before action by the Assembly and the Board in late 1989 or early 1990.

Every member of APA is welcome to attend any meeting of APA's components, except meetings of the Ethics Committee and Ethics Appeals Board or when a component goes into executive session. Your strong support is deeply appreciated; your recommendations for consideration by the Board or other components are most welcome.

Thank you for the privilege and honor of serving as your Secretary for the past 4 years. I have enjoyed the many opportunities to work with you and have learned in a very real and practical way that the greatest resource of the American Psychiatric Association is its members.

SUMMARY OF ACTIONS

ABPN

1. Established the six-member Ad Hoc Committee to Develop a Slate of Candidates for Election to the ABPN (charge outlined in the minutes) (Dec. 1988).
2. Authorized the Council on Medical Education and Career Development, once the American Board of Medical Specialties approves establishing a certificate of added qualifications in geriatric psychiatry, to communicate to the ABPN APA's support for requiring experiences in internal medicine and neurology for those who will undertake the examination for such added qualifications (Dec. 1988).
3. Nominated Dr. Gary Tucker for a second term as a director of the ABPN (June 1988).
4. Nominated the following APA members for election to the Committee on Certification in Child Psychiatry: Drs. Taghi Modaressi, Mohammad Shafii, and Alayne Yates (Dec. 1988).

Advocacy Project

1. Renewed the Ad Hoc Committee for the Pilot Advocacy Project for another year (June 1988).
2. Instructed legal counsel to prepare adequate documentation concerning limiting liability for the Pilot Advocacy Project (June 1988).

Affiliated Organizations

1. Contributed $10,000 from the Board contingency fund to the American Psychiatric Association Auxiliary and requested that the Committee of Friends meet with the auxiliary to develop jointly a long-term strategy for the auxiliary's growth and development (March 1989).

Aging

1. Endorsed the statement prepared by the Task Force on Alzheimer's Disease and forwarded it to the editor of the *American Journal of Psychiatry* for consideration as an editorial; discharged the task force with gratitude (June 1988).
2. Approved the nomination of Dr. Gene Cohen for the Allied-Signal Achievement Award for Public Policy in Health Care for the Aging and approved the nomination of Dr. Marshal Folstein for the Allied-Signal Achievement Award for Achievement in Biomedical Research (March 1989).
3. Approved for publication the report of the Task Force on Nursing Homes and the Mentally Ill Elderly, with the following stipulations: 1) staff must carefully review the document and make necessary editorial changes, 2) the chairpersons of the Council on Aging and the task force must approve these changes, and 3) APA and the American Association of Retired Persons should determine how best to use the report in working with Congress (March 1989).

AIDS

1. Renewed the Ad Hoc Committee on AIDS Policy for another year (June 1988).
2. Authorized spending $7,500 from the Board contingency fund to support a special meeting of the Committee on Psychiatric Aspects of AIDS (June 1988).
3. Established the Commission on AIDS (responsibilities outlined in the minutes); disbanded with appreciation to the members the Ad Hoc Committee on AIDS Policy and the Committee on Psychiatric Aspects of AIDS (Sept. 1988).
4. Authorized APA to cosponsor the AMA International Conference on Counseling, Testing and Early Care, which will be held immediately before the fifth International Conference on AIDS in Montreal in June 1989 (March 1989).
5. Approved "Interim Guidelines for Psychiatrists Who Are HIV Infected" and "Interim Guidelines for HIV Infection in Outpatient Psychiatric Services" (Sept. 1988).
6. Authorized the President of APA to send a letter of congratulations and support to Admiral James Watkins and members of the President's Commission on the HIV Epidemic (June 1988).

Amendment to Constitution and By-Laws

1. Approved an amendment to the APA By-Laws, chapter 3.2, that would allow the Speaker-Elect to vote at meetings of the Board of Trustees in the Speaker's absence; authorized the reading of the amendment to the membership at the 1989 annual meeting before placement of the amendment on the 1990 ballot (March 1989).

American Journal of Psychiatry

1. Appointed Drs. Paula J. Clayton, Arnold M. Cooper, Howard H. Goldman, and David J. Kupfer to 4-year terms as Associate Editors of the *American Journal of Psychiatry*; their terms will begin at the end of the 1989 annual meeting (March 1989).
2. Passed a resolution expressing to the family of Dr. Morris Lipton APA's condolences and appreciation of Dr. Lipton's significant contributions to the Association over the years, especially his recent work as Deputy Editor of the *American Journal of Psychiatry* (March 1989).

American Medical Association

1. Authorized the Medical Director to expend funds to support Dr. John McGrath in his candidacy for AMA Trustee (Dec. 1988).
2. Ratified the Executive Action authorizing APA cosponsorship of the AMA's 9th National Conference on the Impaired Health Professional, held in Chicago on Oct. 26–30, 1988, and selecting Dr. Stephen Scheiber as the APA representative to the AMA conference planning meeting (May 1988).
3. Ratified the Executive Action authorizing Dr. Sabshin to respond to the AMA's request for input regarding the advisability of urging the World Health Organization to develop a clinical modification of *ICD-10* (June 1988).
4. Approved continued financial support of the AMA/Specialty Society Medical Liability Project and authorized a $2,500 contribution to the project from the 1988 Board contingency fund (Dec. 1988).
5. Approved APA's participation in the development of an AMA report on the effects of changes in the medical environment on psychiatry (June 1988).

American Psychiatric Press, Inc.

1. Approved reappointment of Dr. Melvin Sabshin to a second 4-year term and appointment of Dr. Doyle I. Carson to complete the term of Dr. William Sorum on the Board of Directors of the American Psychiatric Press, Inc. (APPI) (Dec. 1988).
2. Approved the reappointment of Dr. Harvey Bluestone to a second 4-year term on the APPI Board of Directors (May 1988).

Annual Meeting

1. Authorized the chairperson of the Committee on Advertising to serve for 2 years on a trial basis on the Committee of Advertisers and Exhibitors as a liaison between the two committees, with the intent of increasing communication and collaboration between the two components (June 1988).

2. Added the following statement to the exhibit rules and regulations: "Attention-getting devices in the form of entertainment or amusement are strictly prohibited in the exhibit hall. The use of magicians, fortunetellers, dancers, mimes, puppet shows or other entertainment of this nature is prohibited. The use of celebrities who are not routinely employed as spokespersons for the exhibiting company is discouraged" (Dec. 1988).

3. Approved development and distribution of an information bulletin at the exhibitors' registration booth during APA meetings (Dec. 1988).

4. Voted to prohibit organizations that discriminate in recruitment or employment on the basis of gender, race, religion, or sexual orientation from recruiting or offering employment in APA exhibit areas, in accordance with APA policy as stated in the 1973 "Position Statement on Homosexuality and Civil Rights" (Dec. 1988).

5. Approved an increase in fees for the annual meeting, beginning in May 1989 (schedule outlined in the minutes) (June 1988).

6. Authorized the Committee on Medical Student Education to seek outside funding of a luncheon for medical students at the 1989 APA annual meeting, following established procedures and working in conjunction with the Medical Director's Office (Sept. 1988).

7. Authorized the Committee on Occupational Psychiatry to seek outside funding for a coffee reception at the 1989 annual meeting (Dec. 1988).

8. Authorized APA to accept outside funding from the Upjohn Company for resident participation in meetings of the Assembly and Board of Trustees and other appropriate meetings held in conjunction with the APA annual meeting (Dec. 1988).

9. Increased the fee for an annual meeting symposium sponsored by a pharmaceutical company from $15,000 to $20,000 for 1990 and to $25,000 for 1991 (Dec. 1988).

10. Ratified the Executive Action authorizing the Assembly Committee of Representatives of Minority/Underrepresented Groups to seek outside funding of a symposium on prejudice (Dec. 1988).

11. Authorized the Committee on Women to seek outside funding for a hospitality suite at the 1989 annual meeting (June 1988).

12. Authorized the Committee of Young Psychiatrists to seek outside funding of a reception for all young psychiatrists attending the 1990 annual meeting (Dec. 1988).

Asian-American Psychiatrists

1. Authorized the Committee of Asian-American Psychiatrists to plan a 2- or 3-day follow-up conference on Asian and Asian-American mental health, with the understanding that the committee would confer with the Council on Internal Organization, the Scientific Program Committee, and others concerning the optimal duration, format, and timing of the meeting; authorized the committee to seek outside funding of the conference (June 1988).

Awards

1. Ratified the recommended recipients of the 1989 APA Distinguished Service Award, namely, Drs. Solomon Snyder and Eric Kandel for the individual awards and both the Robert Wood Johnson Foundation and the American Association of Chairmen of Departments of Psychiatry for the institutional awards (Sept. 1988).

2. Ratified the Executive Action changing the Psychiatric Institutes of America Foundation Award for Research Development in Hospital Psychiatry from an award to an award/fellowship (Dec. 1988).

3. Ratified the Executive Action authorizing acceptance of funding for 5 years from the Dista Products Company in support of the APA/Dista Products Resident Research Award (formerly funded by Pennwalt Corporation and known as the APA/Pennwalt Resident Research Award) (Dec. 1988).

Children and Adolescents

1. Created the Ad Hoc Committee on Psychiatric Hospitalization of Adolescents and charged it with preparing an initial statement on the appropriate admission of adolescents, with the understanding that, if necessary, the statement could be approved through the Executive Action mechanism in consultation with additional Board and Assembly leaders; further, requested this group to prepare a position statement, with input from the Council on Children, Adolescents, and Their Families, for action by the Board and Assembly (March 1989).

2. Approved publication of the revised report of the Task Force on Clinical Assessment in Child Custody, titled "Child Custody Consultation," pending funding (June 1988).

Components

1. Established the following components: Board of Trustees—Ad Hoc Committee to Revise Procedures for Nominating the Member-in-Training Trustee-Elect (Sept. 1988), Ad Hoc Committee on Composition of the Board (Sept. 1988), Ad Hoc Committee on Conflicts of Interest (Sept. 1988), Ad Hoc Committee to Develop a Slate of Candidates for Election to the ABPN (Dec. 1988), Ad Hoc Committee on Psychiatric Hospitalization of Adolescents (March 1989), Ad Hoc Committee to Evaluate Quality Assurance Activities (March 1989), Ad Hoc Committee on Legislation Affecting Quality of Care (March 1989); Council on Economic Affairs—Work Group on the Harvard Resource-Based Relative Value Scale Study (June 1988); Council on International Affairs—Task Force on Conflict Resolution (Dec. 1988); Council on Medical Education and Career Development—Committee of Young Psychiatrists (Sept. 1988); Council on Research—Task Force on Quantitative Electrophysiological Assessment (March 1989); special boards and components—Commission on AIDS (Sept. 1988), Work Group on National Data Bases in Psychiatry (March 1989).

2. Renewed the following components: Ad Hoc Committee on AIDS Policy (June 1988), Ad Hoc Committee on Guidelines for Executive Sessions of the Board of Trustees (June 1988), Ad Hoc Committee on Liaison Activities (June 1988), Ad Hoc Committee for the Pilot Advocacy Project (June 1988), Ad Hoc Committee to Study Officers' Meetings and Other Board Retreats (June 1988), Ad Hoc Committee on Subspecialization (June 1988).

3. Made the following changes to existing components: Board of Trustees—changed the name of the Board Committee on Professional Liability Insurance to Board Committee on Insurance and authorized the committee to oversee all APA insurance programs, the APA Insurance Trust, and Professional Risk Management Services, Inc. (PRMS), and designated the Committee on Member Life, Accident, and Health Insurance and the Risk Management Committee on the APA Insurance Trust subcommittees of the Board Committee on Insurance (Sept. 1988); Council on Internal Organization—moved the Committee on Member Life, Accident, and Health Insurance from the Council on Internal Organization to the Board Committee on Insurance (Sept. 1988), changed the Subcommittee on Telemedical Services to a committee (June 1988); Council on Medical Education and Career Development—authorized changing the name of the Selection Advisory Committee of the Minority Fellowship Program to the Selection/Advisory Committee of the APA/NIMH Minority Fellowship Program and authorized changes to the charge (Dec. 1988), authorized changes to the charge of the Committee on Consultation-Liaison Psychiatry and Primary Care Education (Dec. 1988).

4. Discharged the following components: Board of Trustees—Ad Hoc Committee to Study the Role, Composition, and Function of the Joint Commissions (June 1988), Ad Hoc Committee to Review Treatments of Psychiatric Disorders (June 1988), Ad Hoc Committee for Potential Restructuring of Marketing Strategies (June 1988), Ad Hoc Committee on AIDS Policy (Sept. 1988); Council on Aging—Task Force on Alzheimer's Disease (June 1988); Council on Children, Adolescents, and Their Families—Corresponding Task Force on Confrontational Therapies (Dec. 1988); Council on International Affairs—Task Force on Problems of Americans Overseas (Dec. 1988), Task Force on Terrorism (Dec. 1988), Task Force to

Plan the Joint Meeting in China (Dec. 1988), Task Force to Plan the World Psychiatric Association Regional Symposium (Dec. 1988); Council on National Affairs—Committee on Psychiatric Aspects of AIDS (Sept. 1988); Council on Psychiatric Services—Committee on Federal Government Health Services (Dec. 1988); Council on Research—Task Force on Sudden Death (June 1988), Task Force on the Use of Laboratory Tests in Psychiatry (Dec. 1988); special boards and components—Group to Plan a Conference on the Future of Psychiatry and Related Activities (May 1988).

Economics of Health Care

1. Established the 1-year, six-member Work Group on National Data Bases in Psychiatry, which will report to the Board of Trustees, will have representation from the Council on Psychiatric Services, Council on Economic Affairs, Council on Research, and the Joint Commission on Government Relations, and will carry out the charge outlined in the minutes; allocated $5,000 from the Board's contingency fund to support the work group in the coming year (March 1989).

2. Approved for publication "Employee Assistance Programs and the Role of the Psychiatrist: Report of the Committee on Occupational Psychiatry" (Dec. 1988) (published in May 1989 issue of the *Journal*).

3. Approved a request from the Institute for Health Policy of Georgetown University School of Medicine for APA to join other medical specialties in endorsing the physician satisfaction project, including the telephone survey, at no cost to APA (March 1989).

4. Reaffirmed APA's commitment to the mission of the quality assurance programs and their importance to the Association (June 1988).

5. Ratified the Executive Action establishing the Ad Hoc Committee to Evaluate Quality Assurance Activities (charge given in the minutes) (March 1989).

6. Approved negotiations with Aetna by the Committee on Quality Assurance to develop criteria and an appeals system for review of claims and independent medical examinations (March 1989).

7. Established the Work Group on the Harvard Resource-Based Relative Value Scale Study within the Council on Economic Affairs (charge outlined in the minutes) and established that it will include representatives from the AMA Section Council on Psychiatry, the Joint Commission on Government Relations, the Assembly, the Board, and other relevant APA components, approved funding an initial meeting of the work group, drawing $4,000 from the Joint Reference Committee's new component fund, $4,500 from the Board's contingency fund, and the expenses for Assembly representatives from the Assembly budget, with the understanding that the work group could request additional funding as needed (June 1988).

8. Approved 2-year funding for consultative services to evaluate the Harvard Resource-Based Relative Value Scale study (Sept. 1988).

9. Authorized spending $21,500 from the Board's contingency fund to support the additional study required by the Work Group on the Harvard Resource-Based Relative Value Scale Study (March 1989).

Education

1. Approved in principle and authorized negotiations with the Dista Products Company for a continuing education project on depression (Dec. 1988); approved a contract with Dista for this project (March 1989).

2. Authorized the Council on Medical Education and Career Development to define the "critical incidents" of psychiatry and to seek outside funding in support of the 2–3-year project (Dec. 1988).

3. Approved the Position Statement on Corporal Punishment in Schools and authorized its distribution to support legislation prohibiting corporal punishment in schools (March 1989).

4. Endorsed an interim response to the authors of "Basic Residency Curriculum Concerning the Chronically Mentally Ill," which would communicate APA's support of increased attention to training in the treatment of the chronically mentally ill (Dec. 1988).

5. Ratified the Executive Action approving APA's recommendations with respect to the proposed changes in "Special Requirements for Residency Training in Psychiatry" and authorizing the Medical Director to send APA's response to the Residency Review Committee for Psychiatry of the Accreditation Council for Graduate Medical Education (March 1989).

6. Ratified the Executive Action approving APA's recommendations with respect to the proposed changes in "Special Requirements for Residency Training in Neurology" and authorizing the Medical Director to send APA's response to the Council of Medical Specialty Societies for its use in responding to the Accreditation Council for Graduate Medical Education (March 1989).

7. Ratified the Executive Action authorizing the Task Force on Post-Residency Fellowship Training to seek outside funding through a grant or contract with NIMH for approximately $10,000 to support a survey of fellowship programs and related costs (Dec. 1988).

Elections

1. Accepted by mail ballot the results of the 1988 election and voted to postpone consideration of disposition of the ballots until its meeting on May 8, 1988 (April 1988).

2. Authorized APA staff to destroy the ballots from the 1988 election immediately after the 1988 annual meeting (May 1988).

3. Approved changes to the election guidelines that would allow APA to make available or sell membership labels, as well as lists, to any APA member for purposes related to elections (June 1988).

4. Revised the procedures for selecting nominees for Member-in-Training Trustee-Elect (March 1989).

Employment Discrimination

1. Adopted a statement against employment discrimination on the basis of gender or sexual orientation (June 1988) (statement published in November 1988 issue of the *Journal*).

Ethics

1. Approved the following addition to section 2, annotation 1, of *Principles of Medical Ethics With Annotations Especially Applicable to Psychiatry*: "Sexual involvement with one's former patients generally exploits emotions deriving from treatment and therefore almost always is unethical" (Dec. 1988).

2. Accepted the final report of the APA/Hastings Conference on Psychiatric Ethics and New Economics, titled "New Mental Health Economics and the Impact on the Ethics of Psychiatric Practice" (June 1988).

3. Amended an action taken in March 1988 regarding indemnifying district branches in lawsuits based on actions related to processing ethics complaints (see minutes for full text of revised statement) (June 1988).

4. Authorized expulsion of the following members from APA and their district branches because of ethics violations: Drs. Edward L. Askren III of the Georgia Psychiatric Physicians Association, Inc., William F. Bahnson from the Massachusetts Psychiatric Society, Willem G.A. Bosma of the Maryland Psychiatric Society, Frederick Greiling from the Michigan Psychiatric Society, Mary Griffin from the Illinois Psychiatric Society, and Laurence Snow from the Psychiatric Physicians of Pennsylvania (June, Dec. 1988, and March 1989).

5. Approved the principle that APA ethics proceedings should include adversarial hearings with due process rights, with the understanding that specific details, including the standard of proof, will be worked out by the Ethics Committee after input from the district branches and that any changes based on this principle will be brought back to the Assembly in May 1989 and to the Board in June 1989 for final approval (Dec. 1988).

6. Endorsed the development of a mechanism to consider requests from district branches for support of some of the costs incurred while holding hearings in compliance with the revised "Procedures for Handling Complaints of Unethical Conduct"; requested that the Budget Committee and Ethics Committee, in consultation with legal counsel, jointly develop this mechanism and the funding for it and return to the Board for final approval (March 1989).

Fiscal Issues

1. Reported out of executive session that the Board approved a 7.5% increase for all member dues categories for the 1989 fiscal year; approved a merit increase in pay for staff that would average 5.25% and a cost of living increase of 4.8% for fiscal 1989 (Sept. 1988).

2. Approved in executive session the 1989 APA budget of $22,952,306 (Dec. 1988).

3. Established an APA checking account at the Wells Fargo Bank of California in San Francisco for cash and checking operations at the 1989 annual meeting (March 1989).

4. Approved the corporate resolution and funds transfer agreement recommended by the Treasurer (June 1988).

5. Ratified the Executive Action revising the APA Retirement and Savings Plan in accordance with the Tax Reform Act of 1986 and approving a change in the matching contributions whereby they would be paid only for those persons who are employed by the Association on December 31 of the year for which contributions are made (March 1989).

6. Ratified the Executive Action directing the trustee of the APA Retirement Savings Plan to enter a guaranteed income contract type of group annuity contract (form CG 300 LIFO), in accordance with the report prepared by the Association's consultant (March 1989).

7. Ratified the Executive Action authorizing the signing of a contract, subject to approval by legal counsel, with Ketchum, Inc., an executive search firm, to assist APA in recruiting the new director of the Office of Development (March 1989).

8. Allocated $6,000 from the Board's 1989 contingency fund to support travel of the two Vice-Presidents, the Secretary, and the Treasurer and requested that in future years the budget reflect a line item for travel by these officers (March 1989).

Governance

1. Called for more frequent consideration of private practitioners from the pool of active APA members for appointments to components and councils and for nominations to APA office and requested the appropriate components to review mechanisms to enable individuals to serve in these roles regardless of their professional affiliations or background (Dec. 1988).

2. Ratified the Executive Action waiving policy in "Operations Manual of the Board of Trustees" to permit the appointment of Dr. Donald Scherl as chairperson of the Work Group on the Harvard Resource-Based Relative Value Scale Study (Sept. 1988).

3. Waived current policy to permit Dr. Harold Visotsky to be reappointed to serve an additional year (through May 1989) as chairperson of the Council on International Affairs (May 1988).

4. Waived policy in the Board's operation manual to permit Dr. Dave Davis to be reappointed as a member and chairperson of the Consultation Service Board and to permit Dr. Richard Lamb to be reappointed as a member and chairperson of the Committee to Coordinate the H&CP Service, Journal, and Institute (March 1989).

5. Established an ad hoc committee of past APA presidents to work with the Council on National Affairs and the Assembly Committee on Minority and Underrepresented Groups to study the composition of the Board to determine whether it has an adequate representational balance (Sept. 1988).

6. Renewed the Ad Hoc Committee on Guidelines for Executive Sessions of the Board for another year (June 1988).

7. Approved "Guidelines for Executive Sessions of the Board" (Sept. 1988).

8. Renewed the Ad Hoc Committee to Study Officers' Meetings and Other Board Retreats for another year (June 1988).

9. Approved a special meeting, chaired by the senior Vice-President, for the 12 elected Trustees (three at-large Trustees, seven area Trustees, and the Member-in-Training Trustee and Trustee-Elect) to review and discuss the report of the officers' meeting during the September 1988 component meetings before the September meeting of the Board (June 1988).

10. With respect to special meetings of officers and the Board, encouraged the President to a) continue to convene a summer meeting of the APA officers, b) hold a special meeting (before the September Board meeting) for members of the Board who did not attend the summer retreat of the officers to allow discussion of the report from the officers, c) hold a midwinter meeting of the full Board of Trustees to allow informal and intensive discussion of issues, and d) convene dinner meetings of the Board throughout the year, both for discussion on specific topics and for social interaction (March 1989).

11. Established an ad hoc committee of past presidents to study issues related to conflicts of interest and to develop, in consultation with legal counsel, recommendations and a document on this subject (Sept. 1988).

12. Referred issues concerning the relationship of district branches to the national APA to the Board's Long Range Planning Committee, the Assembly Committee on Planning, and the Joint Commission on Government Relations, with the understanding that legal counsel would be sought as necessary, for development of guidelines for legislative activities and to the Treasurer and the Budget Committee for assessment of fiscal implications (June 1988).

13. Approved a cycle of review and evaluation of the editors of the APA periodicals, i.e., in the third year of editorship and every 5 years thereafter (May 1988).

14. Disbanded the Ad Hoc Committee to Study the Role, Composition, and Function of the Joint Commissions with gratitude and referred the remaining issues concerning liaisons to the joint commissions to the Long Range Planning Committee, the Assembly Committee on Planning, and the officers' meeting for further discussion (June 1988).

15. Asked the Medical Director and staff to review the current Association policies regarding resource development and to present a report to the Board along with options for developing a broad set of policies (Dec. 1988).

16. Encouraged Trustees-at-Large to attend meetings of Area councils outside their areas of residence when such meetings are held in conjunction with the annual meeting; authorized spending up to $2,400 from the Board's 1989 contingency fund to support attendance of each Trustee-at-Large at one additional Area council meeting during the year (Dec. 1988).

Hospital & Community Psychiatry

1. Reappointed Dr. Carl Salzman to a second 4-year term and appointed Drs. Robert E. Hales and Leonard I. Stein to 4-year terms on the editorial board of *H&CP* (May 1988).

2. Increased registration fees for the H&CP Institute (as outlined in the minutes), effective with the 1989 institute (Dec. 1988).

Insurance Programs

1. Modified the APA major medical insurance program to provide a lifetime cap on inpatient psychiatric treatment, noting that the Executive Action mechanism could be employed to set the specific amount after further consultation (March 1989).

2. Charged the Board Committee on Professional Liability Insurance with management and oversight of the APA Insurance Trust and the APA Professional Liability Program, including responsibility for liaison and interface with PRMS and other related groups; asked the Medical Director to develop a staff structure, including an ombudsperson, and reporting lines within APA to support these activities; and voted that financing for the committee and staff is to be derived from the APA Insurance Trust (June 1988).

3. Voted that members of the Board should receive copies of all form letters sent by PRMS in mass mailings to subscribers of APA insurance programs (May 1988).

4. Changed the name of the Board Committee on Professional Liability Insurance to the Board Committee on Insurance; designated the Risk Management Committee on the APA Insurance Trust a subcommittee of the Board Committee on Insurance; charged the Board Committee on Insurance with oversight of the APA member life, accident, and health insurance program, designating the Committee on Member Life, Accident, and Health Insurance a subcommittee of the Board Committee on Insurance and authorizing funding for these activities from the APA Group Insurance Trust (Sept. 1988).

International Affairs

1. Discharged the Task Force on Problems of Americans Overseas with an expression of the Association's appreciation (Dec. 1988).

2. Discharged the Task Force to Plan the Joint Meeting in China with an expression of great appreciation to its members for an excellent scientific program at the meeting in Beijing in August 1988 (Dec. 1988).

3. Established the 2-year, six-member Task Force on Conflict Resolution within the Council on International Affairs (charge outlined in the minutes) (Dec. 1988).

4. Authorized the Council on International Affairs and staff to propose to the Educational Commission on Foreign Medical Graduates that APA become a major consultant in the International Medical Scholars Program; authorized the Task Force on International Education to enter into this agreement and to report to the APA leadership on the final mechanism that will be used in implementing this consultation (Dec. 1988).

5. Authorized the Council on International Affairs to pursue the possibility of a joint meeting with the Royal College of Psychiatrists in 1992 (Dec. 1988).

6. Discharged the Task Force on Terrorism with an expression of the Association's appreciation (Dec. 1988).

7. Nominated Dr. Harold Visotsky for office in the next Executive Committee of the World Psychiatric Association (WPA) and authorized the Medical Director and the Council on International Affairs to select a specific office in coordination with other member societies of the WPA (June 1988).

8. Approved Dr. George Tarjan as nominee for the WPA committee representing the United States (March 1989).

9. Discharged the Task Force to Plan the World Psychiatric Association Regional Symposium with an expression of the Association's appreciation (Dec. 1988).

Judicial Actions

1. Approved the recommendation of the Commission on Judicial Action not to fund the California ECT litigation in the absence of an affirmative recommendation by the California Psychiatric Association (June 1988).

2. Approved a contribution of up to $5,000, on a matching basis, to the California Psychiatric Association for its amicus brief in *Reese v. St. Mary's Hospital*, a right to refuse treatment case (Sept. 1988).

3. Approved APA's role as an amicus in the California Supreme Court hearing of *CAPP v. Rank* and voted to establish a small group of APA members with whom the Commission on Judicial Action could consult about policy issues during the preparation of the brief (Sept. 1988).

4. Authorized payment of $3,500 to the Washington Psychiatric Society for one-half of the cost of its amicus brief for *In re Bryant*, a District of Columbia right to refuse medication case (June 1988).

5. Authorized payment of $5,000 to the Florida Psychiatric Society for reimbursement on a matching basis for its amicus brief in *Paddock v. Chacko*, a case that addresses psychiatrists' duty to commit "suicidal patients" (Dec. 1988).

6. Approved a contribution of up to $5,000, on a matching basis, to the North Carolina Psychiatric Association for its amicus brief in *In re Lynette H.*, a case involving validity/invalidity of the juvenile commitment standard of the state (Sept. 1988).

7. Authorized payment of $5,000 to the New York Psychiatric Association for reimbursement on a matching basis for its amicus brief in *Savastano v. Nurnberg*, which involved opposing judicial procedures for the transfer of committed patients from city to state hospitals in New York (June 1988).

Legislation, Federal

1. Recommended that the Joint Commission on Government Relations examine carefully the concept of actuarial equivalence with the intent of supporting its use in legislation regarding insurance coverage of mental illness to secure maximum flexibility in treatment options, recognizing that APA should continue to lobby for nondiscrimination in coverage for mental illness and should be cognizant of the importance of APA input to current legislation (June 1988).

2. Voted that no action be taken on the Kennedy-Waxman legislation regarding minimum health benefits legislation (S. 1265) which could tie the hands of the APA negotiators (March 1989).

3. Approved a resolution supporting the Senate Labor and Human Resources Committee Reported Minimum Health Benefits for All Workers Act of 1988 (S. 1265, Senate Calendar Number 691, Report 100-360), stating the following positions: 1) APA's support does not diminish its pursuit of nondiscriminatory treatment of mental illness, 2) APA continues to encourage and urge a waiver where state laws mandate a mental health benefit that is greater in amount, duration, and scope than provided in the reported bill, 3) APA supports the concept of actuarial equivalence, which prohibits any trade-off between mental health and other benefits but allows and encourages insurance plans to provide, as the mental health benefit alternative, actuarially equivalent, patient-appropriate mental health treatment modalities, and 4) APA supports the inclusion of medical management visits to a physician for the treatment of a mental disorder without any special limits, in addition to mental health benefits otherwise allowed (June 1988).

4. Voted to support the concept of legislation that requires health coverage for all employed persons; while recognizing that APA must continue to pursue nondiscriminatory coverage for mental illness, instructed the Joint Commission on Government Relations to lobby actively to amend S. 1265 to include a waiver permitting states which currently have mandated insurance benefits higher than those in S. 1265 to maintain or increase those required benefits; authorized and encouraged APA lobbying in all states to provide higher levels of coverage than in S. 1265 (June 1988).

Liaison Activities

1. Renewed the Ad Hoc Committee on Liaison Activities for another year (June 1988).

2. Established formal liaison with the International Psychogeriatric Association at no cost to APA (March 1989).

3. Approved the recommendation of the APA representatives to the Nominating Committee of the Council of Medical Specialty Societies that Dr. Carol C. Nadelson be nominated for reelection to a full term on the Accreditation Council for Graduate Medical Education (June 1988).

4. Approved the nominations of Drs. Sara Charles and Carol Nadelson to the Board of Directors of the Council of Medical Specialty Societies (March 1989).

5. Established official liaison between the Society of Military Psychiatrists and the APA Committee on Psychiatric Services in the Military (Dec. 1988).

6. Endorsed APA cosponsorship of the 1989 National Conference on Medical Education and Research in Substance Abuse, which is scheduled for Nov. 7–10 (March 1989).

Member Benefits

1. Endorsed a pilot project in two district branches to provide financial services to members and authorized a contract with Raymond James Financial, Inc., and Grande Financial Services, Inc., to provide these services with the understanding that a) the contract must be approved and signed by the Medical Director in consultation with legal counsel and b) the Committee on Special Benefit Programs will monitor this program in concert with Grande and report back to the Assembly and Board (Dec. 1988).

2. Authorized the Committee on Special Benefit Programs to seek outside funding to support a pilot program to produce seminars for residents on career choices in psychiatry (Dec. 1988).

Member, Honoring

1. Voted to send APA's best wishes to Dr. Karl Menninger on the occasion of his 95th birthday, July 22, 1988 (June 1988).

Membership Actions

1. Approved advancement of 210 members to Fellow status and deferral of decisions on advancement to Fellowship of 31 members; approved 28 individuals for initial membership and advancement; deferred the decision on advancement of one member (names on file) (Dec. 1988).

2. Authorized dropping from APA two members whose dues were in arrears for 1986; authorized dropping from APA membership 370 members whose dues were in arrears for 1987; authorized administrative reinstatement of those returning to good standing in the district branch and APA (names on file) (June, Dec. 1988).

3. Approved the waiver or reduction of APA dues or the transfer to Inactive status for 295 members, as recommended by the Committee on Membership; deferred dues payments for four members; denied 16 requests for dues waivers; denied refund of APA dues to one member (June, Dec. 1988).

4. Approved the policy of dropping from APA membership any Member-at-Large (outside the United States) or Corresponding Member who moves into the jurisdiction of a district branch and fails to apply for district branch membership within a year (Dec. 1988).

5. Approved changing the date of termination of membership for nonpayment of dues from December 31 to June 30 and approved recommendations for implementation; further, asked the Committee on Constitution and By-Laws to review chapter 8, section 7, of the By-Laws in light of this change to determine if any amendment needed to be made to the Constitution and By-Laws (Dec. 1988).

6. Approved a revision of the operations manual to exempt members who are fully retired from practice from the requirement of holding a valid medical license (Dec. 1988).

7. Approved a revision to the operations manual that would allow residents enrolled in a 1-year primary care training program that will be followed by a 3-year psychiatry residency to be eligible for Member-in-Training status (Dec. 1988).

8. Authorized dropping APA members who did not meet the dual membership requirement and authorized administrative reinstatement for those returning to good standing in the district branch and APA (names on file) (June, Sept., Dec. 1988 and March 1989).

9. Authorized dropping from APA membership as of Oct. 1, 1988, a member whose license to practice medicine had been revoked (name on file) (Sept. 1988).

10. Approved a request from a member of the Genesee Valley District Branch that his advancement to General Member status be made retroactive because of a delay in processing; the district branch recommended approval since it claimed responsibility for the delay (name on file) (Dec. 1988).

11. Deferred a request from the Michigan Psychiatric Society that the membership of Lafayette Clinic–VA Medical Center residents be made retroactive to 1985 (names on file) (Dec. 1988).

12. Denied requests from two members of the Southern California Psychiatric Society for exemption from the dual APA/district branch membership requirement (names on file) (Dec. 1988).

13. Denied two applications for Associate Membership submitted by members in the Oregon Psychiatric Association and the Northern California Psychiatric Society and an application for advancement from Member-in-Training to Associate Member from a member in the Southern California Psychiatric Society, on the basis that the individuals did not meet the criteria for membership; considered the transfer application of an Associate Member who joined APA in 1975 through the Eastern Missouri Psychiatric Society but whose application for transfer to the Orange County Psychiatric Society was rejected on the grounds that the member did not seem to meet the criterion of training or experience in psychiatry, and approved the transfer since the decision on membership eligibility was made in 1975 and could not be changed retroactively (names on file) (Dec. 1988).

Planning, Long-Range

1. Approved the content of "Statement of Mission, Goals and Objectives of the American Psychiatric Association," which represents a consensus of positions, with the understanding that the wording may be altered slightly to improve the text (June 1988).

2. Recommended to the Long Range Planning Committee that much greater attention be paid to the needs of underrepresented and minority populations and international concerns in all the goals and objectives covered in "Statement of Mission, Goals and Objectives of the American Psychiatric Association"; requested the Long Range Planning Committee to return the revised statement to the Assembly along with the rationale for deciding how these needs have been addressed in the revised statement; voted that APA should include a proper reflection of the international interest of the Association in its overarching mission and goals and requested the Medical Director to explore and initiate the appropriate process to accomplish this (Dec. 1988).

3. Reinforced the 1987 Board vote to "encourage APA members to donate 5 percent of their clinical practice to providing voluntary nonreimbursed care to members of minority and underrepresented populations" and urged APA members to offer pro bono services (Dec. 1988).

Psychiatric News

1. Approved the following rotation of terms for membership on the *Psychiatric News* Editorial Advisory Board: effective May 1989, Dr. George Tarjan will be reappointed for 4 more years, Dr. Harvey Ruben for 3 more years, Dr. William Sorum for 2 more years, and the lay editors (Mr. Dick Walt and Ms. Barbara Culliton) will remain indefinitely (June 1988).

2. Appointed Mary Jane England, M.D., to the Editorial Advisory Board for *Psychiatric News* to fill the vacancy created by the death of William Sorum, M.D. (Sept. 1988).

3. Approved the following addition to the section on *Psychiatric News* in "Operations Manual of the Board of Trustees": "News reports, commentaries, editorials, and the like in *Psychiatric News* do not reflect official policies of APA unless the text of the report specifically so indicates" (March 1989).

4. Approved the following addition to the section on the *Psychiatric News* Editorial Advisory Board in the Board's operations manual: "The chairmanship of the [Editorial Advisory Board] shall be held by one of its members, as recommended by the editor-in-chief, when a vacancy occurs in this position" (March 1989).

5. Approved text (given in the minutes) describing *Psychiatric News* and the Editorial Advisory Board for insertion in the operations manual (June 1988).

Psychiatric Services

1. Approved for publication "Guidelines for Psychiatric Practice in Community Mental Health Settings" as a joint task report from the Task Force on Professional Practice Issues in Organized/ Managed Care Settings and the Assembly Task Force on Community Mental Health Centers, with the understanding that this does not set a precedent and that similar reports in the future will be considered on a case-by-case basis (Dec. 1988).

2. Adopted the "Guidelines for Psychiatrists' Signatures" and requested that, to achieve broad distribution, these guidelines be published in the Official Actions section of the *American Journal of Psychiatry* (March 1989).

3. Approved the "Position Statement on Psychiatric Services in Jails and Prisons" (adopted by the Assembly in November 1988) (Dec. 1988) (published in the September 1989 issue of the *Journal*).

4. Approved for publication the report of the Task Force on Jails and Prisons (March 1989).

Public Affairs

1. Ratified the Executive Action providing $2,000 from the Board of Trustees' contingency fund to pay for an ad in the *New York Times* for Mental Illness Awareness Week (Dec. 1988).

2. Referred to the Budget Committee, for consideration during development of the 1990 budget, a request for $5,000 to support the Daniel Yankelovich Group's survey of public attitudes toward mental illness (March 1989).

Religion and Psychiatry

1. Approved for publication the report of the Committee on Religion and Psychiatry, titled "Cults and New Religious Movements" (June 1988).

Research

1. Authorized the Task Force on DSM-IV to seek funding from the MacArthur Foundation to support research activities for *DSM-IV* (March 1989).
2. Ratified the Executive Action authorizing the Office of Research and the Office of Minority and National Affairs to respond to a request for proposals from NIMH by submitting a research training proposal for a grant-supported project designed to increase the numbers of underrepresented minorities entering and remaining in psychiatric research (Dec. 1988).
3. Authorized the APA Office of Research to accept a grant from NIMH for the assessment of mental health research funding outside of NIMH (March 1989).
4. Established the 2-year, four-member Task Force on Quantitative Electrophysiological Assessment within the Council on Research (charge outlined in the minutes) (Dec. 1988).
5. Approved "Procedures for APA-Conducted Studies and Projects" (included in the minutes) (June 1988).
6. Discharged the Task Force on Sudden Death with gratitude (June 1988).
7. Authorized the Office of Research, in conjunction with Policy Resources, Inc., and NIMH, to survey psychiatric faculty and to accept outside funding to support the services provided by the Office of Research (Dec. 1988).

Report of the Treasurer

Alan I. Levenson, M.D.

This report is prepared from audited figures for the fiscal year that ended Dec. 31, 1988. The data presented also appear in the auditor's annual report. Table 1 is a statement of our financial condition, taken from the independent auditor's report, and table 2 reflects functional revenues and expenses. These will provide the membership with the information needed to assess the operation and financial condition of the Association.

Fiscal Status as of Dec. 31, 1988

During 1988, APA again was able to live within its means by establishing clear goals and using our limited resources to achieve those goals. As a result, APA's financial position at the end of 1988 remained strong in terms of the results of operations, net worth, cash flow, and debt reduction.

The operation of APA programs during 1988 resulted in income of $22,244,937 and expenses of $21,823,678, for a surplus from operations amounting to $421,259. Of this amount, $300,000 had been included in the 1988 budget as planned surplus for debt reduction. The remaining $121,259 represents surplus beyond that called for in the operating budget.

Services for members. APA's most important function is service to its members. Our membership increased from 24,676 members at the end of 1978 to 35,168 at the end of 1988, for an average net gain of over 1,000 members per year. The overall increase in the last 10 years was 42.5%, but this growth rate was not equally distributed among the various categories of membership: the number of Members-in-Training (residents) has grown by 288%, while General/Associate Members and Fellows have increased by 15%. The enrollment and continuing membership of medical students and residents have important implications for the future growth and strength of the Association.

APA began enrolling Medical Student members in 1984. Since that time, membership in that category has grown from 208 to 676, and it now accounts for 2% of the total membership. Medical students are becoming an important source of new Members-in-Training: 103 medical students were advanced to this status in 1987 and 136 in 1988.

There are currently 5,638 Members-in-Training, representing 16% of the membership. Residents are fast becoming the most important source of new General Members; while the number of new General Members each year tends to remain stable, the proportion of those who become General Members by advancement has grown significantly, from 56% of new General Members in 1984 to 78% in 1988. For example, 820 Members-in-Training were advanced in 1987 and 922 in 1988.

Our larger membership, our strong financial base, and the increasingly complex problems and opportunities facing our profession have led to the development and provision of expanded services for APA members. This growth in services has been primarily in the areas of government relations, public affairs, education, Office of Member Services activities, economic affairs, and research.

Net worth. The Association's stated net worth has increased from approximately $4 million in the mid-1970s to over $11 million today ($11,104,926). This stated figure is extremely conservative, since it does not include the estimated increase in the value of the 1400 K Street property that APA purchased in 1980. If this estimated increase in land value were to be included as part of APA's stated net worth, the figures would stand at about four and one-half times our net worth in the mid-1970s. Even with the impact of inflation, the increase in the Association's net worth in recent years is particularly impressive: from $7,486,501 in 1984 to $8,439,044 in 1985, $9,823,172 in 1986, and $10,702,311 in 1987. This represents an average increase in net worth of approximately $1 million per year during that 3-year period. The Association realized an additional increase in net worth during 1988 of $402,615.

Debt reduction. During 1985 APA negotiated an excellent loan package with the National Bank of Washington and has since renegotiated even more favorable terms. Highlights of the loan package as it is currently configured are as follows:

1. *Term loan*—$1,500,000 at ¾% over the prime rate. As of Dec. 31, 1988, $975,000 of the loan had been retired, leaving a balance to be repaid of $525,000.
2. *Line of credit*—maximum of $3,000,000 at ¼% over the prime rate. The stability of the cash budget was evidenced by the fact that the line of credit was used during only 6 weeks of 1988 and only $500,000 of the line of credit needed to be used.

The term loan is scheduled to be completely retired as of September 1990, which will meet the most conservative definition of being debt free. However, another debt reduction bench mark has already been met on schedule. As originally projected, the Association's short-term investment portfolio exceeded the term loan balance in

TABLE 1. APA Balance Sheet as of Dec. 31, 1988 and 1987

Item	1988	1987
Assets		
Current assets		
Cash and cash equivalents	$ 3,151,536	$ 3,003,800
Marketable securities	651,533	447,518
Accounts receivable, less allowance for doubtful accounts	1,492,767	1,444,095
Grants and contracts, approved and in process	2,190,029	1,875,870
Notes receivable	395,000	149,000
Publications inventory	494,111	231,691
Prepaid expenses and other current assets	348,214	415,100
Total current assets	8,723,190	7,567,074
Property and equipment		
Land	5,187,470	5,187,470
Building—leasehold interest and improvements	6,884,724	6,525,413
Furniture and equipment	2,262,249	1,898,379
Subtotal	14,334,443	13,611,262
Less accumulated depreciation and amortization	1,939,439	1,538,621
Total property and equipment	12,395,004	12,072,641
Other assets		
Notes receivable, less current maturities	330,173	726,000
Deferred expenses, net of accumulated amortization	1,612,431	570,536
Deferred land rent	724,182	686,832
Advances to affiliates	210,732	267,270
Nonmarketable securities	125,000	125,000
Total other assets	3,002,518	2,375,638
Total assets	24,120,712	22,015,353
Liabilities and fund balances		
Current liabilities		
Current maturities of long-term debt	300,000	325,000
Accounts payable	1,863,666	1,454,948
Accrued expenses	1,780,539	1,470,028
Deferred revenue	2,288,598	1,533,149
Deferred amounts		
Restricted—grants and contracts	334,862	294,824
Restricted—awards and special projects	1,461,160	1,243,727
Total current liabilities	8,028,825	6,321,676
Other liabilities		
Advances from affiliate	306,943	—
Long-term debt, less current maturities	225,000	525,000
Capital lease obligation, less current maturities	4,455,018	4,466,366
Total other liabilities	4,986,961	4,991,366
Fund balances		
Unappropriated	6,842,371	6,421,112
Appropriated	150,000	150,000
Building	4,112,555	4,131,199
Total fund balances	11,104,926	10,702,311
Total liabilities and fund balances	24,120,712	22,015,353

December 1987. The bench mark is significant since it represents the point at which it was possible for APA to repay the entire loan from proceeds of the short-term portfolio. The Association has met its obligations under the loan package since its inception.

TABLE 2. APA's Functional Revenues and Costs for Fiscal Years 1988 and 1987

Item	1988	1987
Functional revenues		
Percent from each function		
Publications		
Advertising	16.02	15.82
Subscriptions and related fees	6.31	5.91
Book sales	22.07	27.38
Member services		
Dues from members	33.90	33.12
Meetings income	9.83	8.72
Other income related to member services	2.75	2.84
Other income (investments, overhead on grants, etc.)	9.12	6.21
Total revenues (dollars)	$22,244,937	$21,445,884
Functional costs		
Percent from each function		
Governance and member component activities (Board of Trustees, Assembly, joint commissions, councils and components)	15.41	12.95
Publications (APA journals and book sales)	34.27	36.04
Public affairs (public information and government relations)	10.30	11.04
Member services (membership services and educational programs)	26.33	26.94
General administrative costs	13.69	13.03
Total costs (dollars)	$21,823,678	$20,614,895

Investments

The Investment Advisory Committee has guided the Association's investment program over the last 13 years. The stated investment policy of the Association is "to employ sound investment vehicles affording maximum return consonant with safety of capital, i.e., the type of investment a prudent individual would seek." With this in mind, safety of capital has been identified as the first objective of the investment program. In 1980, the Association carefully reviewed its investment alternatives and shifted a majority of its investment resources from ownership of securities to an ownership position in the new headquarters building project. The investment portfolio, as distinguished from the investment in the APA office building, currently stands at approximately $650,000.

The current policy of the Association is to balance investments between debt instruments and common stocks. In the portfolio valuation of Dec. 31, 1988, approximately 70% of the portfolio was invested in debt instruments, 1% in cash and accrued interest, and 29% in stocks. The Association's investment portfolio is under continuing review and is subject to change in response to changing market conditions.

Publications

Psychiatric News generated income of $2,900,651, contrasted with expenses of $1,347,269, for a surplus of $1,553,382. This amount is $374,849 more than the budgeted surplus of $1,178,533.

The *American Journal of Psychiatry* produced revenues of $2,437,716 and incurred expenses of $1,731,439, for a surplus of $706,277. This total is $298,817 more than the budgeted surplus of $407,460. The journal *Hospital & Community Psychiatry* realized revenues amounting to $1,021,777 and expenses of $861,793, for a surplus of $159,984.

The Association and its publishing affiliate, the American Psychiatric Press, Inc. (APPI), maintain approximately 250 book titles in inventory. In 1988, total income for the APA publication program (excluding APA periodicals) amounted to $7,297,569. Of this total, $4,909,828 was provided by sales of APA publications and products and $2,387,741 was accounted for by APPI book sales.

A Note of Caution

In my report to you last year, I sounded a note of caution that still applies to the financial position of the Association. Specifically, a strong fiscal position at the end of 1988 does not mean that we can relax our efforts in sound fiscal planning, effective program management, and vigorous monitoring of expenditures. The same hard work that enabled the Association to achieve its stable financial situation will be needed to maintain it. For example, our ability to produce income is essential to our fiscal strength, but our income depends on many factors outside our direct control. The nonrenewal of a contract or delay in a publication schedule could lead to a significant shortfall in projected income. For example, APA and Intracorp mutually agreed to terminate the contract under which APA has been providing quality assurance services for Intracorp. This has resulted in a transition period for that program. The Association's leadership is currently reviewing this program in terms of both its fiscal and its programmatic aspects.

Conclusion

Traditional indicators of fiscal status point toward a financially strong APA as of Dec. 31, 1988. Our operating surplus, net worth, cash flow, debt reduction, and investment portfolio all point to fiscal health. This financial strength is the foundation for a wide variety of programs for our members and our patients, and it provides the resources through which we are meeting the needs stemming from our rapidly changing environment.

Our sound financial position has been developed over the course of many years. During that time we have put in place and refined a number of outstanding programs for our members and patients, entered into a partnership involving a successful building program, and developed productive nondues income sources. The financial aspects of our operation have been developed in tandem with our professional activities and, in essence, represent different sides of the same coin. It is important that we continue the thoughtful approach to the operation of our Association which has led to our programmatic and financial success. We must continually review the needs facing our membership and be prepared to refine the objectives we have established to meet those needs when necessary. We must prioritize the many competing claims on our limited resources, and we must closely monitor our activities to ensure that what we do is in keeping with these priorities.

I am delighted to have the opportunity to provide you with this positive financial report and to work with you in meeting the challenges that face our Association.

Report of the Medical Director

Melvin Sabshin, M.D.

During my 15 years' tenure as Medical Director of APA, the annual report has become a useful reflection of progress and problems. We have indeed been coping with extraordinary challenges; the themes of socioeconomic and political ferment have dominated my reports for some time. The coping process has been accompanied by a steady growth in our membership and an increased diversity and complexity of the functions assumed by the national leadership and the Central Office. In following up on last year's report, I am pleased with the mood, strength, and stability of the organization. Both the tone and content of our activities are positive overall and demonstrate strong, effective working relationships between staff and members. Dr. Fink's energetic and effective leadership and strong interests in so many internal, as well as external, areas is reflected in the expansion and enhancement of many departments' efforts.

While the quantity of work at the Central Office continues to increase, we have been able to maintain quality, even in the face of increasing demands in many arenas. This year, APA has focused on how to provide the best support and leadership for the diverse needs of the more than 35,000 members while avoiding fragmentation due to the increasing interest in subspecialization and the many forms of practice. We also have been concerned with developing strength and expertise in our subsidiary and business-related work, as well as the more traditional specialty society efforts. To that end, we have held frequent discussions with our counterparts in other medical specialties and in the other mental health disciplines.

Staff changes highlight the balance between stability and growth. I am quite sad to report the death of Morris Lipton, Ph.D., M.D., Deputy Editor of the *American Journal of Psychiatry*, in March 1989. Dr. Lipton brought special knowledge and warmth to the *Journal* and will be greatly missed.

In July 1988, Dr. John M. Hamilton joined the staff as Deputy Medical Director and Director of Psychiatric Services, succeeding Dr. Donald W. Hammersley, who retired in January 1988. Dr. Hamilton is a vigorous staff leader who has taken active responsibility for many areas, including the Institute on Hospital & Community Psychiatry, the H&CP Service, the placement service, the excellent conference on managed care, and the complex and demanding aspects of our quality assurance efforts. I have appointed Ms. Corky Hart as Associate Director of the Office of Psychiatric Services and am especially appreciative of her quiet but effective leadership, not only there but in the work of the Joint Reference Committee.

In April 1989, Ms. Kathleen Bryan retired as Director of the Office of Meetings Management after 20 years of service to APA. Kathleen has been a unique contributor to our work and a recognized national leader in her specialty. I have appointed George Campbell, formerly Exhibits Manager, as Director of the office and am pleased at the smoothness of the transition.

In January 1989, John Bonnage, Ph.D., a long-term staff member and Director of our AIDS Education Project, accepted a position with the state of New Jersey to coordinate education on the acquired immune deficiency syndrome (AIDS). Under his able direction, our AIDS activities became a valuable and effective part of Association functioning. Ms. Carol Svoboda has been appointed director of our professional education project, and Ms. Jackie Moore has assumed the newly created role of coordinating efforts related to AIDS policy.

This year, Dr. John Nemiah completed 10 years of service as

Editor of the *American Journal of Psychiatry.* His editorship has brought exciting changes to both format and content while he has maintained the scholarly base and readability that have been hallmarks of the *Journal* over the years. We are most pleased with the outcome of the transition begun when Ms. Melanie Shipley succeeded Ms. Evelyn Myers as Managing Editor upon Ms. Myers' retirement.

Still another transition was the departure of Ms. Teddi Fine, Assistant Director of the Office of Research, who previously served as Associate Director of the Division of Government Relations. Teddi was a unique contributor to our work, and we are most pleased that she agreed to remain a consultant until this May, providing her special expertise in support of our Council on Aging. She will continue to be available to APA as a consulting writer/editor. Ms. Brenda Overman has been appointed Assistant Director of the Office of Research, while Ms. Ellen Smith has assumed responsibility for the Council on Aging.

Last year I introduced Dr. Thomas Dial, Assistant Director for Research Studies in the Office of Research, who joined us from the Association of American Medical Colleges. This year I am pleased to inform you that the 1,943-page *American Psychiatric Association Biographical Directory 1989* has just been published and is available for your use. This directory represents an extraordinary data collection effort and provides considerable information about our members. Dr. Dial will be overseeing the analyses of demographic and practice information provided by respondents.

Another transition I mentioned last year was the promotion of Dr. Carolyn Robinowitz and the subsequent appointment of her successor, Dr. Philip G. Bashook, as Director of the Office of Education. Dr. Bashook has rapidly established himself as a leader in psychiatric education. Under his leadership, the Office of Education has begun several new initiatives: assessing members' needs and interests in continuing medical education and determining how best to meet them, exploring innovative learning/teaching modalities, publishing a pamphlet for residents on how to teach, developing new evaluation approaches for our meetings, identifying necessary characteristics of postresidency fellowship training, and planning a study of critical incidents in psychiatric education and practice. The office also supports publication of the *Psychiatric Knowledge and Skills Assessment Program (PKSAP).* The sixth edition of *PKSAP* is an impressive compendium of the knowledge of the field and a stimulating approach to self-learning.

Dr. Robinowitz has expanded her functions as my deputy and alternate in many settings. Her new role reflects some of the internal staff reorganization, which we expect to continue. On a number of occasions I have commented on the increased complexity of our functions and the ongoing need for reevaluating the structures and functions of the Central Office. Not too many years ago, we were more like a "mom and pop" store. There were advantages and disadvantages to such a system. Staff knew each other better, and our managers could tolerate more informality. While we have not yet become a super-modern "business office," we are beginning to use technology and information systems better. Dr. Robinowitz has been working with me to analyze the changes in staff and function resulting from our growth over the past decade and to develop a more rational internal staff organization, using a system of clusters of departments, offices, and divisions and reporting practices that will increase efficiency and enhance internal communication. She has strengthened interoffice working relationships and communication, leading to even more integrated approaches to function and administration, as well as our health policy efforts. Further efficiency measures and reorganization will be needed, but I still enjoy writing individual letters, meeting as many APA members as I can, and visiting district branches to learn firsthand about issues members face and their proposals for the future.

There has been a major resurgence of interest in the governance process over the past year. The increased activities of the Assembly Executive Committee and its evolution as a major force in the governance of the Assembly of the Association were reflected in its interim meeting in September 1988, the very successful joint meeting with the Joint Reference Committee in February 1989, and its expanding role in assisting the Assembly in planning and implementing actions. The Joint Reference Committee, too, has strengthened the input of the voting members while maintaining the importance of the participation of council chairpersons, emphasizing its role as "joint," representing both the Assembly and the Board. The Joint Reference Committee increasingly acts not simply as a referring body but also as an initiator and developer of proposals and directions. Drs. Edward Hanin and Gerald Flamm are to be congratulated for their thoughtful yet pragmatic approach to both issues and processes.

The officers of the Board and Assembly again held two planning meetings this year. These efforts reflect the increased involvement and interest of the officers, the expanded amount of business on the agenda of each Board meeting, and the need to set time aside for reflection and strategic planning for the Association. The Board of Trustees has discussed how best to involve area Trustees, Trustees-at-Large, and the Member-in-Training Trustee in this process. To that end, an ad hoc committee of the Board has been formed to review these functions and make recommendations for possible modifications.

This interest in organization and function is reflected in the ongoing discussion of subspecialization and liaison by the Assembly and ad hoc committees of the Board. Last year district branches and psychiatric organizations were surveyed to determine their perspectives on organization, representation, and governance. A meeting chaired by President Fink was held with leaders of key psychiatric organizations during the Institute on Hospital & Community Psychiatry. The meeting itself was well attended, and participants' recommendations have formed the basis for much work since. The American Board of Psychiatry and Neurology has responded positively to our recommendation to initiate the process for offering a certificate of added qualifications in geriatric psychiatry. In continuing to explore these issues, we will be cognizant of the potential fragmentation and divisiveness of such efforts and the need to maintain organizational strength while maximizing the input of all concerned.

Last year I introduced Dr. Allen Frances, who chairs the Task Force on DSM-IV. During the ensuing year, there has been an extraordinary amount of activity in this area, and the various work groups have been formed. The publication *DSM-IV Update,* which is available from the Office of Research, provides excellent information on process and content. The oversight Committee on Diagnosis and Assessment in the Council on Research, chaired by Dr. Layton McCurdy, will provide policy direction and leadership. Dr. Frances continues to meet with the Assembly, Board of Trustees, and other member components to report and receive input. Dr. Harold Pincus and his staff have been invaluable in providing coordination and support for these important activities. The process has focused on the best integration of research and clinical directions in nomenclature and diagnosis, and by providing representation and oversight throughout we hope to maintain a high degree of member involvement.

This effort is another example of the productivity and stature of our Office of Research. Working closely with the late John Adams, M.D., the energetic and productive chairperson of the Council on Research, Dr. Pincus and his staff have generated many new ideas, convened meetings of a variety of research constituencies, and developed and strengthened valuable links with a number of professional and consumer groups. The continuing excellence of the *Psychiatric Research Report* is a source of great pride and satisfaction.

We have learned that effective June 1, 1989, the Health Care Financing Administration will require that diagnostic codes submitted by physicians to Medicare be official *ICD-9-CM* codes. Fortunately, the majority of codes in *DSM-III-R* already are compatible with *ICD-9-CM.* The only change in psychiatrists' office operations will be to eliminate fourth- and fifth-digit zeros from some *DSM-III-R* codes and to substitute new codes for eight diagnostic categories. By now all APA members should have received an adhesive-backed listing of the codes that require minor alteration. This listing can be attached to *DSM-III-R.* We continue to work with key Congressional leaders to eliminate the extra administrative step of dropping fourth- and fifth-digit zeros from certain codes.

In previous annual reports, I have given special emphasis to our activities in government affairs and public affairs. This year is no exception; indeed, I still rate these areas as having the highest priority because of their ability to produce genuine advances in diminishing stigma while increasing access to and reimbursement for care.

Working in concert with our Joint Commission on Government Relations, Dr. John J. McGrath, chairperson, and the other commissioners and network leaders, our Division of Government Relations continues to function as a sophisticated, effective force.

From my perspective, during this past year we have been much more visible and successful in our government relations activities than ever before. We have begun to develop clear and concrete objectives that have had an enormous impact on our members and the patients we treat.

The Kennedy-Waxman (now Kennedy) proposed legislation on mandated insurance coverage continues to spark much debate, as its content raises certain conflicts for the Association. Jay Cutler has been instrumental in negotiating the inclusion of mental health benefits—none were contained in earlier versions. Of continued concern is the level of mental health coverage specified by the federal mandate, which makes more care available to the entire population but overrides state mandates, a few of which require greater coverage than the federal mandate. This discrepancy has led to a fear that some programs may lower their coverage. We will continue to monitor the legislation closely and work to improve benefits for psychiatric care.

The extraordinarily successful Federal Legislative Institute was held in Washington in March 1989. District branch representatives heard presentations on a broad array of issues from key legislators and staff. Dr. James McDermott, a psychiatrist and newly elected Democratic representative from the state of Washington, was the keynote speaker at the meeting of the Corporation for the Advancement of Psychiatry. Also speaking were Silvio O. Conte (R–Mass.), who received the first federal Jacob Javits Award in recognition of his strong support of psychiatric research.

This year has seen an increase in the amount and contentiousness of activities by the American Psychological Association in their efforts to expand the scope of psychologists' licensure and services. In addition to their efforts in *CAPP v Rank*, we have seen attempts in state legislatures to add hospital privileges to psychologists' scope of practice. Further, the attempt to gain authorization to prescribe psychotropic medication—supported in part by the Department of Defense interest in a pilot study of such privileges—has raised serious concerns about the potential impact on patient care. No matter how collaborative individual professional relationships have been, psychiatrists, who are well aware of the potential problems, side effects, and interactions of psychotropic medication, express horror at the possible involvement of insufficiently trained personnel in prescribing.

The American Psychological Association has been most vocal in supporting the expanded scope of psychologists' practice, although its members are divided as to its extent. It is ironic that the psychologists strongly espouse psychological rather than pharmacologic care and are quick to point out some of the problems in using medications. The psychologists' sense of battle with psychiatrists is expressed in their press release regarding the settlement with the American Psychoanalytic Association (of which APA was not a part), which emphasized a victory over the psychiatrists. I personally have been more involved in national and local debate and testimony than ever before. The resignation last summer of the Executive Director of the American Psychological Association, Dr. Leonard Goodstein, and the wait for a permanent successor has made it difficult to initiate productive staff communication on these issues.

I want to commend Joel Klein and his staff and the many staff and members who contributed to our excellent brief on *CAPP v Rank*. Its focus on the importance of education to quality of care was so strong that the American Association of Chairmen of Departments of Psychiatry also endorsed it—the first time they ever have participated as an amicus curiae.

We continue to oppose efforts to expand the scope of psychologists' practice involving Medicaid recipients (the Coyne and Rockefeller bills). We are especially concerned that the proposed legislation would permit direct reimbursement for mental health care without requiring medical assessment and development of a differential diagnosis and medical treatment plan for this especially vulnerable population.

We are most fortunate to have Jay Cutler leading our government relations efforts. He is widely respected not only on Capitol Hill and in the Administration but by his colleagues as well. Our successes are a credit to his energy and knowledge, as well as to the involvement of the field in communicating with Congress.

We also have been active in other government arenas. This year the appropriations for the National Institute of Mental Health (NIMH) increased at the highest percentage ever, documenting Congress's increased appreciation of psychiatric research. Dr. Fred Goodwin was appointed Administrator of the Alcohol, Drug Abuse, and Mental Health Administration. The appointment of a senior scientist to this position reflects the directions of the field and the impact of research advances in psychiatry. Increased interest in funding for substance abuse disorders is vital, and to strengthen such support we work closely with Dr. Goodwin and with Drs. Schuster and Gordis, the Directors of the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, respectively.

At the same time, we must not lose the momentum gained during the past 2 years in support of psychiatric research in NIMH. We are very pleased with the creative leadership of Dr. Lewis Judd, who is in his second year as Director of NIMH. He has a wealth of experience and leadership in the research arena and is sensitive to future needs. Dr. Judd, in collaboration with the National Mental Health Association, has initiated a National Mental Health Leadership Forum, whose members represent major professional organizations and advocacy groups. This group is planning a "war on mental illness" through a strong public and professional educational campaign. I look forward to its work and to our participation in it.

Last year, I alerted you to the upcoming Harvard study of reimbursement for practice activities. The resulting resource-based relative value scale (RBRVS) has spawned much discussion and controversy in medicine. The results of the study of psychiatry were flawed, in part because they were based on the existing *Physicians' Current Procedural Terminology* (*CPT*) codes for psychiatry. It was quite apparent that the *CPT* is highly inadequate for the current practice of psychiatry. We have communicated to the AMA *CPT* Editorial Board the recommendations of our committee studying procedural terminology for expansion and clarification of the codes for psychiatry. Additionally, NIMH has made funds available for a revised study of psychiatry based on these expanded procedural codes. We are promoting implementation of the recommended changes and working to ensure a more valid study.

Under Dr. McGrath's leadership as our delegate to the AMA, the work of the Section Council on Psychiatry and the visibility and effectiveness of psychiatry in the House of Delegates committees too has expanded. The active involvement of the American Academy of Child and Adolescent Psychiatry and our representatives to the Resident Physicians' Section and the Young Physicians' Section has been productive. Our joint meeting with the AMA Board of Trustees in December 1988 was most fruitful, and we are pleased to work with the AMA Council on Long-Range Planning in preparing a report on the future of psychiatry. Dr. McGrath's excellent contributions have been evident in his membership on the AMA Council on Legislation and his leadership of reference committees. This year his candidacy for the AMA Board of Trustees is an exciting challenge. Mr. Cutler has worked most effectively with AMA staff in the legislative arena, and I have enjoyed and profited from my meetings with AMA Executive Vice-President Dr. Sammons and other specialty society staff. Ms. Carol Davis has provided highly sophisticated and effective coordination of all our efforts with the AMA and has truly been the "connective tissue" integrating all these functions.

We have been similarly successful in our public affairs functions. In his capacity as chairperson of the Joint Commission on Public Affairs, Dr. Harvey Ruben has provided energetic and wise leadership, working with Mr. John Blamphin, who heads our staff division. Collaborative projects with industry have assisted in enhancing psychiatry's image with other physicians and the public. The joint effort with the Upjohn Company will support APA production of three films for public education. The first film produced in this venture, "Panic Prison," has been well received by viewers. Development of a similar film on anxiety has also begun. We now have an experienced network of trained leaders who can cope effectively with all varieties of media. The biannual Public Affairs Network Institute held this year was most productive. Participants developed a series of agendas, directions, and priorities for national and local efforts. We plan to increase our proactive involvement with the media in the year to come.

Under Paul Fink's leadership, we are continuing our campaign against stigma. Mental Illness Awareness Week is an excellent model for interdepartmental and interorganizational collaboration and highlights the importance of work with consumer advocacy groups. This year there was a considerable increase in publicity and interest of professionals, media, and the public. The very successful seminar "Advances in Research and Clinical Care" was held on Capitol Hill, and over 100 members of Congress, staff, and community representatives attended.

Of our more than 35,000 members, over 5,300 are residents. This year marked the first official service of a Member-in-Training Trustee and Member-in-Training Trustee-Elect on our Board of Trustees. There has been increased active resident participation in the Assembly and area councils, and formation of a component for/on young psychiatrists, which both interacts with its companion component on young physicians in the AMA and addresses the particular needs and issues related to the practice of younger psychiatrists. Our retention of residents after training is excellent, and the Board of Trustees demonstrated its awareness of special issues for this population by adopting a graduated dues schedule for the first years after residency.

Our yearly census of all psychiatry residents documents the increasing interest of medical students in psychiatry. This year, for the first time in a decade, there was a slight drop in the number of medical students choosing first-year positions in psychiatry through the National Resident Matching Program, although the proportion remained essentially the same. We will pursue both data and rationale in the upcoming months. Psychiatry residents also noted greater satisfaction with their field (considerably fewer transferred to other specialties) and greater interest in combined residencies or postresidency subspecialty training. The residents themselves are bright and articulate and bring a special vitality to the Association.

Dr. Marta DeLalla has been a most effective Director of the Office of Member Services. She and her staff have made a special effort not only in recruitment and retention of members and in maintaining a strong working relationship with the district branches but also in providing the highest quality communication and services to our members. Our studies of member retention (at all levels) have emphasized the importance of the district branch dues structure in membership stability. We also recognize that some areas of the country (e.g., Area VI) are experiencing a "graying" of the membership and increases in the numbers of members being elevated to Life status, so district branches are providing costly services with less dues income to support them. We are cognizant of the impact of this demographic change, and Dr. DeLalla is working with the membership committees to address this issue.

Also gratifying has been the significant number of members who vote in our elections for APA officers and Trustees. This year, of those eligible, 5% more voted than did so in 1988, and the actual number of members voting (15,518) was an all-time high. We remain one of the few large national organizations that conducts a contested election and opens voting to the entire membership.

While Dr. Jeanne Spurlock and her staff have been active in many areas, providing voice, support, and recognition of issues affecting minorities and children and their families, their contributions to the residents' fellowship programs have been especially meaningful to these colleagues and to those of us who interact with them. We await with concern the NIMH decisions on funding for the minority fellowship program—a program that has had much positive impact on the residents and, especially, the field.

This April Dr. Spurlock was one of the APA representatives on a medical mission of inquiry to South Africa. Cosponsored by APA and the American Association for the Advancement of Science, its goal was to determine how the South African emergency legislation affected the provision of medical services. Dr. Spurlock also has been especially involved in a number of representational and liaison efforts dealing with medical, mental health, and advocacy groups, and she has been a most effective spokesperson.

This is Dr. Allan Tasman's first year as chairperson of the Scientific Program Committee. Under his direction, the program at the annual meeting continues to expand in content and increase in sophistication. There has been greater attention to integrating research findings into the scientific educational program and an increasing emphasis on interactive and participatory sessions for clinicians. The annual meeting is a high point of the year's functions. It is a mirror of directions for the field and a proactive and integrating force. The 1989 scientific program theme, "Overcoming Stigma," has generated much interest, and the meeting's multiple sessions and formats address this and other important topics. Advance registration for the meeting and enrollment in the continuing medical education courses have been the highest ever. Joined by members of the Scientific Program Committee and the Local Arrangements Committee, Dr. Tasman has already begun planning for the 1990 meeting in New York City, which promises to be of very high quality as well.

None of the success of the annual meeting would have taken place without the devoted efforts of the staff. In particular, I would like to recognize Ms. Carol Davis, who has provided oversight and support as well as her special know-how and experience in so many areas, staff of the Office of Meetings Management, and the remarkable organizational efforts of Cathy Earnest, who heads the Office to Coordinate the Annual Meeting. Their creativity and resilience enable us to handle this complex, multifunctional, and large-scale event in a way that provides each attendee the opportunity to have an enjoyable and useful educational and social experience.

We similarly are pleased with the Hospital & Community Psychiatry Institute. Not only did the 1988 Institute in New Orleans attract a record number of attendees, who participated in over 180 presentations, but the participants' high degree of satisfaction reflected the depth and diversity of program content and the opportunities for active interaction among attendees and presenters. There was a record number of meetings of allied professional organizations, and under the leadership of President Fink a meeting of psychiatric subspecialty groups addressed issues related to subspecialization and interorganizational relationships.

The journal *Hospital & Community Psychiatry* also has grown in quality and stature and reflects the scientific directions of the field. The excellent working relationship between the Managing Editor and Editor, Ms. Teddye Clayton and Dr. John A. Talbott, respectively, has been a model of staff and member collaboration. Similarly, *H&CP* provides a positive model of interdisciplinary collaboration.

The *Psychiatric News* Editorial Advisory Board, chaired by Dr. George Tarjan, has been reviewing both the policies and content of *Psychiatric News.* Consultants from other publications (e.g., *Science, American Medical News*) have provided valuable input. Under the leadership of Dr. Robert Campbell and Mr. Herbert Gant, *Psychiatric News* has increased its emphasis on meeting members' informational needs.

One of the most exciting events in the past year was the 2-day conference on managed care, chaired by Dr. Naomi Goldstein. This participatory conference addressed such areas as treatment, quality of care, impact on psychiatrists' practice, training, and legislation. We anticipate that proceedings will be available late in the year.

The APA Ethics Committee continues to address the future of psychiatric practice and the impact of the new economic systems on care. To that end, the committee has been discussing ethical issues involved in psychiatric hospitalization, especially for children and adolescents. It also has been asked to address ethical issues related to subspecialty practice. Its Subcommittee on Education of Psychiatrists on Ethical Issues is completing a second videotape on undue familiarity between therapist and patient, focusing on treating and reporting. The demands on the Ethics Committee and its staff have been increased in quantity and complexity, and I want to commend Dr. Robert McDevitt, who assumed the chair this year, Ms. JoAnn Macbeth, its legal counsel, and Carol Davis, who provides sensitive and sensible support to the Ethics Committee and Ethics Appeals Board in their excellent work.

We have been very pleased with the development of our Office of Information Systems. Under the leadership of Dr. William More, we have developed innovative approaches to information services for our members. Our ability to communicate and to collect and retrieve information has expanded immensely. Although we are just beginning to use the available technology, APA has been cited as a showpiece specialty society by the Digital Equipment Corporation, on the basis of our excellent, user-friendly format for registration for the annual meeting, as well as the ongoing routine work of the association regarding member communication, dues billing, accounting and financing, and so forth. Dr. More, who is nationally recognized as a medical statistician, has been an excellent resource in our information activities. Recently, he has been especially useful as a resource to the Office of Quality Assurance in developing needed software for their new activities. We hope next year to bring you a report on greater expansion in that area. We believe that in the future, communication and information will be an increasingly important base of our functioning.

Ms. Zing Jung and her staff in the Library have been instrumental in bringing information to our members. Working with Dr. More, they have developed data bases containing APA position statements, prepared indices of our actions and of articles in *Psychiatric News*, and engaged in literature searches and prepared bibliographies at members' request. Such efforts are unique and highly valued by the recipients, who through our Library have access to the full range of the literature and information available. The initiation of the Marion Kenworthy Learning Center in the Library has enhanced our capacities to assist our membership and memorializes an important leader. Drs. Viola Bernard and Martha Kirkpatrick were extremely effective in spearheading the fund-raising for this important project, and we owe them our gratitude as well.

I also am mindful of many members and staff who have devoted their energy and wisdom toward integration, coordination, and unity. In a very special way, Ms. Jeanne Robb and staff in the Office to Coordinate the Board and Assembly epitomize the many functions carried on within APA. They promote the best in our governance and ensure strong links between the members and staff.

Also deserving of special mention this year is the sustained, remarkably high-level contribution of Joel Klein (and other members of the law firm Onek, Klein & Farr). We have found them available in so many activities. I will touch on Mr. Klein's work on professional liability later in this report, but he also deserves praise for his work with our Commission on Judicial Action. Dr. Paul Appelbaum has been a most effective leader of this component, addressing a broad array of legal and judicial issues. Mr. Klein has been a valued friend and counselor through a number of difficult and thorny decision points.

Among my own special areas of interest, a number of international responsibilities are to be noted. I particularly have enjoyed being active in the World Psychiatric Association (WPA) and chairing the work group charged with preparing a new structure for the organization. Our Office of International Affairs has expanded its efforts and gained wide respect under the leadership of Ms. Ellen Mercer, and this remains a source of special pride and satisfaction for me. The WPA regional symposium held in Washington, D.C., in October 1988 and hosted by APA contained a most stimulating program; there were over 300 scientific presentations and representatives from 32 countries. Our joint meeting with the Chinese Medical Association, held in August 1988, included 100 APA members and approximately 250 Chinese psychiatrists and provided a stimulating and invigorating experience and interchange with our Chinese colleagues. Ms. Mercer and her staff have provided assistance for psychiatrists in this country and abroad with education, transcultural practice, and mental health care issues.

Ms. Mercer was a consultant to the U.S. Departments of State and Health and Human Services in the planning and implementing of the March 1989 visit of two dozen psychiatrists, lawyers, and other experts to the Soviet Union for the purpose of examining current and past patients involuntarily committed to mental hospitals allegedly for political or religious purposes. In October 1988 the newly named All Union Society of Psychiatrists and Narcologists of the U.S.S.R. applied for membership in the WPA, an application that will be acted on by the membership in Athens in October 1989. Our position on that action will be strongly influenced by the final report of the delegation, and we look forward to its publication in June. Specific details of that visit must await completion and publication of the delegation's report, but I am especially grateful to Ms. Mercer, Mr. Klein, and Dr. Loren Roth, whose contributions were essential to its success.

Last year I discussed the appointment of past APA President Dr. Carol C. Nadelson as Editor-in-Chief of the American Psychiatric Press, Inc. (APPI). In the past year, she has been extremely active, not only in broadening and strengthening APPI's ongoing work but also in outreach to develop strong working relationships with potential authors in this country and abroad. The APPI Editorial Board has been expanded to include experts in a variety of clinical areas. Under the able guidance of Mr. Ron McMillen, APPI has begun publication of journals, and this expanding effort will provide an opportunity for leadership in such areas as neuropsychiatry, psychosomatic medicine, psychiatric education, and psychotherapy. Our expanded marketing efforts have already resulted in new directions and greater income. In its 7 years of existence, APPI has become well recognized and highly regarded in the publishing industry. Not only does it have a competitive edge in psychiatric publications, as evidenced by book reviews and sales, but its products also provide an opportunity for scientific education and negate some of the stereotypes about psychiatry and psychiatric patients.

This success reinforces my earlier comments to the Budget Committee and Board of Trustees that budget planning based on subsidiary or business performance must be considered in light of longer-range performance and that every year may not be a good year. While some members described APPI's successes in publications as a windfall, it is important to keep these activities in perspective and to avoid overspending during a year of prosperity or, conversely, pessimism or despair when times are tight.

Our corporate activities raise concern as well as interest. As we become more involved in business-related issues, the realities of implementation pose problems that we must address in both a businesslike and professional manner and with sensitivity to the special needs of our membership.

The crisis in medical liability has been marked by questions about the availability and costs of general liability insurance in this country, which have a profound impact on many APA functions and activities. Just a few years ago, we had major problems obtaining needed liability insurance for our members. A separate corporation was formed—Professional Risk Management Services, Inc. (PRMS)—which provides important cost containment for our membership. As a separate and young corporation, PRMS has faced problems with accountability and availability of insurance for all members, and it must deal with questions about issues in such specific areas as administration and general medical care.

In reviewing the formation and growth of PRMS, special acknowledgment must be given to Joel Klein, APA Treasurer Dr. Alan Levenson, and the APA members involved in the many insurance committees for their extraordinary efforts. Our active efforts in this area have been vital to our members' practice.

Last year I reported on problems with billing for liability insurance renewal and communication with PRMS. The formation of an oversight committee within the Assembly Executive Committee, under the wise leadership of past Speaker Irvin Cohen, and the increased involvement of the Board Committee on Insurance has led to a clearer working relationship between APA and PRMS and to greater sensitivity to the communication process. While some problems still persist, the overall picture is positive.

Special note also should be made of the contributions of Ms. Elizabeth Thomas who, in addition to her role as Assistant Director of the Office of Member Services, also serves as the "ombudsperson" for APA members in insurance-related matters. Liz has developed a strong working relationship with PRMS and has been extraordinarily helpful in addressing and solving problems with communication and information. Through her efforts, the number and intensity of complaints related to insurance matters has fallen considerably.

Efforts in quality assurance have long-range organizational implications. Not only is it appropriate for us to be strong advocates for high-quality psychiatric treatment, but we must endorse appropriate accountability in justifying the medical need for psychiatric treatment. As an organization, we must continue to address questions about confidentiality, utilization, both prospective and retrospective review, and managed care. These are not simple issues with readily visible solutions, but I remain convinced that these programs have been a strong force in maintaining third-party coverage for psychiatric care.

These quality assurance efforts have been closely linked to corporate efforts and the business world. We (and they) have enjoyed financial growth for several years. In so doing, APA, through its commitment to first-rate professional peer review, provides a very high-quality product but is also competing with other groups (some of which include APA members), who use less senior and lower salaried personnel for the review process.

The Office of Quality Assurance is in a phase of transition, from the era of the Intracorp activities, which provided preadmission certification and concurrent review, to independent provision of these services in the open marketplace. The office continues to conduct and review business under the existing CHAMPUS contract, and is responding to a new CHAMPUS request for proposals. After termination of our contract with Intracorp and as our review business winds down, there has been a major increase in marketing efforts—promotion, sales, and advertising services for APA's programs—to pursue replacement business opportunities under the name "AdvancedPsych Systems, a Division of the American Psychiatric Association." On the basis of a market analysis, we have hired a Director of Promotion and Development for Quality Assurance. Efforts in this direction seem positive and have resulted in possible contracts with Prudential, Mutual of Omaha, and some of the smaller "Blues."

These changes can provide both opportunities and problems and necessitate a careful look at expenditures and potential income. To that end, we have completed a business plan that examines the fiscal implications and alternatives related to these new directions and enables us to determine the long-term costs of such ventures in a volatile market. We must be prudent and not risk the Association's assets. Nonetheless, if patient care benefits are to be maintained or expanded in the treatment of mental disorders, it is vital that a competent quality assurance program which assures resources are used as medically necessary is available to third parties and managed care entrepreneurs. Not only does APA thus have a role in developing and supporting appropriate standards of care, but we can ensure that the field is not left to organizations which emphasize cost containment irrespective of quality. Our involvement also allows us to give educational feedback to providers, negate myths about length or outcome of psychiatric treatment, and influence policy makers as to the limits and effectiveness of treatment for mental disorders.

Because this transition is at a critical time for all quality assurance efforts, I have assigned Dr. Hamilton to undertake direct operational responsibility for the Office of Quality Assurance. He has made a number of internal modifications in structure and reporting that are designed to improve function and efficiency while minimizing expenditures. We have reviewed the results of an external audit completed by McGladrey and Pullen, CPA, and have used their assistance in preparing a business plan. Additionally, an ad hoc committee chaired by Dr. Donald Scherl is reviewing the policies and performance of our quality assurance program, considering the environment and marketplace in which we function, and developing a series of options and recommendations for future efforts.

In my judgment, none of these many functions could be carried out effectively without a sound fiscal structure. This is a monumental effort. As we have become involved in a variety of activities that are more difficult to predict than our more circumscribed objectives of only 5 years ago, we depend heavily on staff coordination and proactive planning. We are involved in a building venture, a publication corporation, an insurance corporation, diverse quality assurance contracts, and many other activities in addition to our more traditional functions. I am very grateful to our Treasurer, Dr. Alan Levenson, the chairperson of our Budget Committee, Dr. Steven Sharfstein, and the many other members who have played key roles in ensuring income for the Association and regulating our expenses. Dr. Jack White, Mr. Robert Milanicz, and the staff involved in budget implementation also have done an excellent job. Mr. David McClanahan has contributed strongly to the smooth day-to-day functioning of my office. Ms. Katherine Chambless has been a marvelous addition to the team. Dr. Robinowitz also has been pivotal in this integrative effort, which, in my judgment, shows APA at its working best.

Of vital importance is the presence of a largely behind the scenes staff member who takes major responsibility for making it all happen. Ms. Carol Davis oversees the functioning of my office and all its related events while at the same time maintaining major staff support for the demanding work of the Ethics Committee, the Ethics Appeals Board, and AMA-related efforts. She has a special ability to develop and implement planning processes and is an extraordinarily knowledgeable and sensitive resource. The nature of her work is such that she rarely receives public attention or recognition, yet her contributions are invaluable, and she has won the trust and respect of us all.

Comments about "the best in the APA" are a good link to my belief that we have been extremely fortunate in our choice of leaders. Our President, Dr. Paul Fink, has been an outstanding President, whose vision, energy, and effectiveness have been so important to our functions and our future. His leadership in the war on stigma and his positive collaboration with a broad range of patient and consumer advocacy groups has strengthened the Association and promoted the best in patient care. The scope of his activities and breadth of his efforts have been a model for us all. Our Speaker, Dr. Jack McIntyre, also has been exemplary. His sensitivity to and knowledge of Assembly moods, directions, and needs reflect his service to the Association and the Assembly and his insightful awareness of the issues facing psychiatry. It has been a privilege to work with all of our members this year toward a stronger and more effective APA, and I anticipate an excellent alliance with our next President, Dr. Herb Pardes, and with our incoming Speaker, Dr. Gerald Flamm, and all the other APA members who serve the Association and the field so ably.

Extensive reports on the individual staff departments are available from the Central Office. They attest to the diversity, enormity, and complexity of staff efforts and demonstrate our commitment to strengthening the field and supporting our members and the patients whom they serve. It is a privilege and pleasure to be Medical Director of such a strong and vital organization.

Report of the Speaker

John S. McIntyre, M.D.

This Speaker's report is a review of some aspects of Assembly structure and functioning. The content of other actions by the Assembly, and more broadly of the Association, for the past year are contained in the various topical reports to the Assembly and are well summarized in the Report of the Speaker-Elect and the Report of the Medical Director.

The Present

Over the past 2 years there have been a number of important developments in the growth of the Assembly, and some additional items involving the structure and function of the Assembly are on the agenda for the May 1989 Assembly meeting.

1. In September 1987 the Assembly Executive Committee met for a day and a half immediately after the fall components meetings. This was the first time there was such a meeting in the fall (similar to the spring calendar) to prepare for the fall area council meetings and to plan for the November Assembly. This meeting is clearly a necessity if the Executive Committee is to become more of a deliberative body and optimally assist and direct the Assembly in its work.

2. In 1987 the Executive Committee began to meet on the Sunday

afternoon immediately after the November Assembly meeting to plan strategy for the implementation of Assembly decisions and recommendations and to consider items specifically referred to the Executive Committee by the Assembly. Hence, there are now six Executive Committee meetings a year (including the two organizational meetings on Friday morning at the beginning of each Assembly meeting). In my opinion, this enhanced Executive Committee activity is crucial to an effective, proactive Assembly that fulfills its major role in the governance of the Association.

3. A further development occurred in February 1989 with the contiguous and overlapping meetings of the Joint Reference Committee and the Assembly Executive Committee. This provided a unique opportunity for these two groups to observe and learn from each other and to hold joint deliberations on two issues—the right to refuse medication and subspecialization—which were very productively discussed. Whether or not this format is repeated (and I hope it is—if not yearly, perhaps every other year), improved communication and enhanced understanding has occurred and will help both bodies over the next few years.

4. In 1988–1989 the pilot advocacy projects have come to fruition. These projects were an outgrowth of an action paper from Area III in November 1986 and are important in terms of both content and process. In two of the three district branches—New Mexico and Washington, D.C.—results have already been substantial. In New Mexico, funds were used to sponsor a series of town meetings for consumers in response to the Governor's initiative to develop a statewide community-based mental health system. These meetings culminated in the formation of the New Mexico Coalition for Mentally Disabled Citizens. In the Washington Psychiatric Society, the allotted monies helped fund an ongoing district branch advocacy project that provides both telephone assistance (during a single call) to consumers seeking information concerning health insurance coverage appeal rights, etc., and more extensive efforts to help a smaller group of patients, for whom a variety of actions have been recommended or pursued. The project in the Georgia Psychiatric Physicians' Association is still evolving and consists of that district branch's cosponsorship of the ongoing individual patient advocacy office operated by the Mental Health Association of Metropolitan Atlanta and plans to expand to a statewide program. The process by which national APA funds are used to help support district branch activities or initiatives ("cost sharing") deserves further exploration.

5. Other recent fiscal developments for the Assembly have been the funding of the Assembly operating fund, which represents recognition by the Budget Committee and the Board of Trustees of the Assembly's occasional need for funds outside the usual budgetary process and the growth of the Assembly budget itself from $367,780 in 1985 to $573,854 in 1989.

6. Over the past year the Assembly has continued to explore its relationship with the councils and components (in addition to the fruitful meeting of the Executive Committee and the Joint Reference Committee). Dr. Roger Peele chaired the Assembly's Subcommittee on Liaisons, which reported to the Executive Committee and subsequently to the Assembly's Committee on Planning, and the recommendations that emerged are part of the report by the Committee on Planning at the May 1989 Assembly meeting. The need for a more specific charge for Assembly liaisons to the components, clarification of the liaison's role in the component's activities (vote, etc.), and recommendations to the Speaker as to which components should have Assembly liaisons are important elements in this report.

7. At the November 1988 Assembly meeting, the chairpersons of the Joint Commissions on Government Relations and Public Affairs had designated seats on the floor of the Assembly to emphasize the Assembly's partial "ownership" of the joint commissions. For the Assembly meeting in San Francisco, in addition to the chairpersons of the joint commission, all council and commission chairpersons have been invited, and those who attend will be available to the Assembly and the area councils (and vice versa) in an attempt to improve communication between the Assembly and the councils and to expedite our shared work.

8. In May 1987 the Assembly was expanded to include a Member-in-Training representative and deputy representative from each area. (Before that time the Committee of Residents had a representative on the Assembly Executive Committee.) Hence, there are now 15 Members-in-Training in the Assembly, i.e., 7% of the Assembly, which does not appear excessive considering that Members-in-Training constitute 16% of the membership.

9. The Assembly Committee on Planning will also recommend to the Assembly in San Francisco that the six current minority/underrepresented groups should each continue to be represented in the Assembly until either the Assembly or the constituent caucus decides that the representation should be terminated. The Assembly Committee on Planning felt that the current formal review every 3 years to determine whether the representation of the group should continue has not been helpful and that the reports to the Assembly should reflect the relevant issues on an ongoing basis.

With the exception of the representatives of the minority/underrepresented groups, the Assembly has remained geographic in its representation, but this basic design is now being questioned.

The Past

At the end of the Second World War there was much dissatisfaction about APA's inefficiency and a concern about the lack of grass roots involvement in the governance of the organization. The emergence of these issues has been well documented by several authors (1, 2). They described the formation of the Group for the Advancement of Psychiatry and the decision to appoint a full-time Medical Director as two major responses to the organizational inefficiencies, both of which had positive impacts on APA's future. As to membership participation in the organization in the early 1940s, little had changed since the turn of the century. As Barton (2) noted, in 1946 some 300 members (or 6% of the approximately 5,000 members of APA) participated in the town meeting type of governance activities at the annual meeting. A reorganization committee was formed and its chairperson, Dr. Karl Menninger, presented a plan in 1948. The plan called for a house of delegates that would set policies and elect the national officers while the Board of Trustees would function as the executive arm of the Association. This proposal was rejected by the membership, but a few years later a more modest proposal was approved, establishing the Assembly of District Branches, which had much less authority than the house of delegates in the Menninger plan. In 1953, the Assembly actually met for the first time (2, 3), and 16 district branches were represented. The group was addressed by President Ewen Cameron, the chairperson of the organization committee whose recommendations concerning an Assembly had been accepted. Almost a decade later, after the Airlie House retreat in 1964, the Reference Committee was formed, consisting of the chairpersons of the six existing councils, the President-Elect, the Speaker-Elect, and the Medical Director. Ten years later there was another impetus to reorganize, leading to the "Key Conference" held in Key Biscayne in March 1975. Another proposal for constitutional changes emerged, and the Assembly was again designated the seat of power in a unicameral model. This proposal did not achieve the two-thirds majority vote of the membership required for constitutional change, but over the last 14 years many of the Key Conference initiatives have gradually been enacted. In January 1983, the (Joint) Reference Committee as it is currently constituted was formed; the Assembly and Board of Trustees each has three votes, the Medical Director has one vote, and the chairpersons of the councils and commissions are ex officio nonvoting members (although the committee generally functions by consensus). Clearly, compared to the original Reference Committee of 20 years earlier, the Assembly's influence has significantly increased.

The Future

A major challenge for the Assembly in the next decade will be to continue to represent the entire membership as the field marches inexorably toward subspecialization and as "special interest" organizations of psychiatrists continue to develop.

In October 1988, at the H&CP Institute, Dr. Paul Fink, as chairperson of the Ad Hoc Committee on Liaisons and as President, convened a meeting attended by leaders of 16 national organizations of psychiatrists. At this meeting the other organizations expressed considerable interest in relating more closely to APA, although there was no consensus as to the nature of the relationship(s).

Dr. Roger Peele, in his brilliant "Lighthouse" paper (4), presented the options available to our Association in relating to these other organizations—liaison, affiliation, and assimilation—and argued convincingly for assimilation. At its February 1989 meeting, the Assembly Committee on Planning recommended that the preferred option might better be named "integration." In an attempt to move the process along, the Committee on Planning is recommending (in May 1989) that "the Assembly vote to support the concept of the integration of special psychiatric professional identities into the APA." Even if the Assembly (and subsequently the Board of Trustees) votes to support this concept, it is clear that the route to achieve that goal remains poorly defined. In June 1988 the Ad Hoc Committee on Liaisons presented four models to the Board of Trustees:

1. Conferences of APA with other psychiatric organizations to explore possible relationships (initial attempts at this were APA's December 1987 Conference on the Future of Psychiatry and the October 1988 meeting of leaders of national organizations of psychiatrists).
2. Expanding the council and component structure to include components charged with policy development and related efforts involving their separate subspecialty areas, and soliciting recommendations for membership of these components from related psychiatric organizations.
3. A new federation of representatives from other psychiatric organizations that would parallel the Assembly and report independently to the Board of Trustees.
4. An expanded Assembly including representation from the other organizations/subspecialty groups.

In last year's Speaker-Elect report (5) I supported model 2, i.e., the reorganization and expansion of our councils. This model is fully compatible with continuation of the largely geographical basis of the Assembly, and as I noted last year, one advantage of geographical representation is that it can be a balance to the increased fragmentation of our professional identity. This type of representation emphasizes that regardless of our subspecialty interests, the uniformity of our core determines that all psychiatrists in a given locale have one representative to our national Association.

Convinced as I am of the validity of these notions, over the past year I have begun to feel (as Dr. Irvin Cohen predicted I would) that I was simply resisting change in the Assembly—perhaps as "Robey's Rangers" attempted to resist reform in the APA structure in the late 1940s (2).

Perhaps there is a way to involve these other organizations in the workings of the Assembly while still maintaining the largely geographical representation. This ambivalence appears to have been reflected in the responses of the district branches to the Committee on Planning survey. As reported to the Assembly in November 1988, a majority (61%) of the responding district branches felt that the Assembly should be involved in providing greater opportunity for input from these subspecialty/special interest groups, but when asked if the Assembly membership should be broadened to provide voice/vote representation for these groups, 39% of the district branches responded "no," 24% responded "yes," and about 35% were undecided.

Our experience with the minority/underrepresented groups might be more carefully considered. It has now been 12 years since minority/underrepresented groups were included in the Assembly, and while the benefits of this inclusion have been substantial, certainly our basic geographical orientation has not been significantly diminished.

In my opinion, cogent arguments can be made for models 2 and 4 (models 1 and 3 I find much less attractive). The time to carefully consider these options is now, and the group to do this work should have broad representation from throughout APA and, as recommended by the Committee on Planning, should be under the leadership of a joint Assembly/Board component. I also agree with the Committee on Planning "that recommendations from this exploration should have as a goal the strengthening of the District Branches" (May 1989 report to the Assembly).

Conclusion

APA is fortunate to have outstanding staff, who are in large part responsible for many of the successes of the organization. Dr. Melvin Sabshin is a gifted leader and an extremely effective Medical Director. His influence over the past 15 years has been extensive not only within the organization but throughout the field nationally and even internationally. Dr. Sabshin and Dr. Carolyn Robinowitz have been extremely supportive of the growth of the Assembly, as have all the Deputy Medical Directors. On behalf of the Assembly, I also thank Ms. Claudia Hart and Ms. Lea Mesner for their dedicated and helpful work with the Joint Reference Committee and the Board of Trustees. We also applaud the efforts of Ms. Carol Davis and Ms. Katherine Chambless in the Medical Director's Office and Mr. George Campbell for all of his efforts with the logistics of our meetings.

It is hard to describe the contributions of Ms. Alison Bondurant, Ms. Amy Conrick, Ms. Lea Mesner, and Ms. Jeanne Robb to the Assembly. Suffice it to say that without the help they provide, the Assembly could not continue to function. The effectiveness of Ms. Conrick and Ms. Robb in working with the Assembly committees and area councils and in facilitating and integrating the Assembly's work with other parts of APA accounts for much of the success of the Assembly in recent years.

It has been delightful as well as inspiring to have been Speaker with Dr. Paul Fink as President. His vigorous leadership, enthusiasm, and dedication to overcoming the stigma of mental illness have been contagious. Working with our distinguished President-Elect, Dr. Herbert Pardes, has also been invigorating, and his contributions to our Association are already substantial.

On behalf of the Assembly, I especially thank the Assembly officers and the Executive Committee for their dedicated and productive efforts. Our Speaker-Elect, Dr. Gerald Flamm, has brought to the Assembly leadership a wealth of experience from many different settings, and this, combined with his boundless energy and facilitating style, has greatly benefited the Assembly and bodes well for the year to come.

Finally, I thank the members of the Assembly for their hard work, support, and encouragement and for honoring me by electing me Speaker of the Assembly. I am deeply grateful.

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Report of the Speaker-Elect

Gerald H. Flamm, M.D.

Moving from the floor of the Assembly to the position of Speaker-Elect was a most exciting and formidable step for me. The headiness of the position was quickly modified by the humility that arose from attending meetings of the Executive Committee of the Assembly. The history, background, richness of the Assembly's activity, and the role of the Executive Committee in implementing the move quickly helped me realize how much I had to learn. I was aided in learning the meaning of the office, the sense of history behind it, and the authority and responsibilities that went with it by contributions from friends and colleagues: Jim Trench, Jack McIntyre, Ed Hanin, Irv Cohen, and Roger Peele.

Being Speaker-Elect carries with it the roles of vice-chairperson of the Joint Reference Committee and chairperson of the Assembly Budget Committee. Both were new experiences for which I turned to Jeanne Robb, especially for help with the budget, and to Corky Hart, for help with the Joint Reference Committee; both provided background that permitted me to exercise my judgment in making decisions. I appreciate this and thank them.

The officers' meeting was exciting, stimulating, and educational. The elected leaders met informally to discuss the issues of priority to APA and learn the President's plans and program for the coming year. Communicating these to the membership, and particularly to the Assembly, was one of the challenges emerging from the officers' meeting. Attendance at the Board of Trustees' meeting revealed the difficulty the Board has in dealing with the innumerable problems that come before it. I was very pleased to be able to attend and emphasize how important it is for the Speaker-Elect to have this experience. The Board makes very agonizing decisions, many of them in the budgetary area. Since budget and program priorities are intertwined, cutting the thorny knot requires almost Solomonese wisdom from the members.

The chairperson of the Joint Reference Committee during the past year has been President-Elect Dr. Herb Pardes, and it was refreshing to see his efficiency and effectiveness at the meetings of the officers, the Joint Reference Committee, and the Board, and it quickly became clear that these qualities, combined with his sensitivity to the diverse membership of the Assembly and APA overall, promised very successful years as President-Elect and President. Working with him on the appointment process reaffirmed my belief in his commitment to excellence and his ability to integrate differing viewpoints into the process. The appointment process is complicated by the large number of outstanding applicants and recommended candidates for a very limited number of vacant slots. In implementing the process, I cannot remember a single point of disagreement with Herb. He always respected my opinion and the role of the Assembly in the operation of APA.

My roles on the Joint Reference Committee and Board of Trustees reassured me of the respect the Assembly has attained with these bodies. While not all the members of the Joint Reference Committee and Board are equally familiar with the Assembly and its operations, there is in general a profound appreciation of the work the Assembly and Assembly Executive Committee do before they refer actions to the Joint Reference Committee and the Board. This year the joint meeting of the Assembly Executive Committee and the Joint Reference Committee was an opportunity for each to see the other in action. Each could appreciate the commitment and seriousness of the roles of both bodies. The Assembly, with its grass roots voice, was respected. Committee chairpersons, who are nonvoting members of the Joint Reference Committee, bring to it the deliberations of their councils on actions referred to them. It became clearer why APA is as effective as it is and why many policies and positions require so much time to come to fruition. The Board has less time to be deliberative at its meetings, and acts after discussing the recommendations brought to it. Board committees are appointed to further explore issues, and a number of joint Board/Assembly committees have developed in recent years. There is no better means of developing mutual respect than having two groups work together on complicated issues; one such example was the committee involved in reviewing Professional Risk Management Services, Inc., and other insurance issues. It was especially rewarding, at meetings of the Board and Joint Reference Committee, to observe how an apparent impasse could be overcome by Herb Pardes' comments or jokes, which relieved the tension and made for a new surge of energy, leading to a relatively quick resolution of the issue or referral for further study.

The increased activity of the Assembly Executive Committee has made functioning as Speaker-Elect a more doable job. In its discussions the Assembly Executive Committee examined the many different sides of issues and problems and illustrated the diversity of opinion within, and across, regions of the country. This both crystalized the Speaker-Elect's role in presenting the Assembly's position and helped me appreciate and represent the diversity within the Assembly. Thus I attained a degree of latitude in a number of issues that came to the Joint Reference Committee. The difference between a nearly unanimous vote in the Assembly and a marginal vote by membership strength is one example of the difference in the force of advocacy. Participation in the activities of the Planning Committee is an indispensable part of the Speaker-Elect's role. Here, Assembly issues of enormous complexity are explored by representatives from the different Areas, Members-in-Training, and minority groups. In this committee, complementary and supplementary positions are reviewed and decisions are hammered out under very able leadership. The committee members deserve a strong pat on the back for their outstanding and committed work. Anyone who has attended a meeting has appreciated that. Two recurrent and related questions are whether the Assembly should be modified, enlarged, or remain as it is and whether the essentially geographic representation should be preserved or replaced. Recommendations will be presented for discussion on the floor. Member-in-Training and minority group input was extremely helpful in broadening the committee's understanding.

Another issue of continued importance to the Assembly is subspecialization. This is different from representation in governance, although the two are often mixed and confused. Subspecialization, so far, has led to Assembly approval for "added qualifications" in geriatrics. Currently, alcohol and substance abuse is knocking at the door, as is the forensic group. There are questions on how to deal with them, and the American Board of Psychiatry and Neurology must be an active player in the decision. Problems related to subspecializations have been ably dealt with by the Ad Hoc Committee on Subspecialization, which past Speaker Jim Trench has chaired. This committee has explored criteria to be used and defined the governance process for pursuing these matters. It would be reasonable to continue this group for another year, and that decision will be up to the Board. It is extremely important for the membership to recognize that the establishment of "added qualifications" will not jeopardize the general practice of psychiatry and will allow for a core of consultants and educators to improve the knowledge about these very important areas of psychiatry. I certainly do not want to see us build a Tower of Babel of such superspecialization that new jargon makes communication impossible.

Liaison affiliation, or representation in governance, is the other element often confused with subspecialization. A number of alternatives have been introduced, such as meeting with specialty organizations, permitting specialized organizations to send representatives to participate in Assembly meetings with courtesy of the floor, and organizing members of the Assembly into caucuses whereby members from specialty fields join together to formulate a position, as was recently done on the "right to refuse treatment" by a group of forensic psychiatric representatives. These issues do not involve the Assembly exclusively and require an overview by the entire Association of the commissions, councils, and general governance. The Assembly struggles with the question of whether the primarily geographic representation should be replaced by another form of representation, such as one based on specialty organizations. This issue will be discussed and debated for several years to come.

A number of significant issues involving quality of care have arisen. One area has been the attempt of psychologists to gain both prescribing and admitting privileges despite the difference in their training from that of psychiatrists. Although psychologists often pose this as "guild conflict," we are clearly dealing with a quality issue. There is an ongoing atmosphere of deprofessionalization, which makes our task difficult. We are sole possessors of the biopsychosocial training and experience that is appropriate for the care of people with mental and psychiatric illnesses. If a slogan is needed, it may be, "A doctor is a doctor is a doctor." Since deprofessionalization is widespread and encompasses all the mental health providers, competition intensifies and guild issues become focal areas of activity. The Committee on Interprofessional Affairs has therefore become an important component in helping reduce conflict and ensure high-quality care for our patients. At the same time we must be accountable for what and how we practice. Some articles and media presentations in the past few years have been critical of some practices of institutions. They have questioned whether certain practices were ethical and whether some commercial-entrepreneurial operations adequately address the needs of the patient and the quality of service. Unless we monitor our own house, we are in jeopardy of being monitored, in a simplistic way, by outsiders who do not have the breadth of understanding that we have as physicians in psychiatry. Professionalism of the medical establishment has already been questioned too much, and this has jeopardized us. Problems involving restraint of trade and due process arise in many areas, one of which is ethics procedures. The government has insisted on adequate protection of the defendant and the Assembly has supported, in principle, the use of an adversary system for ethics procedures. Since one's capacity to earn a living is involved, the latitude of the past, wherein a professional organization could identify which members it did and did not want, has been narrowed considerably. Unless an adequate process is implemented, restraint of trade can be charged. This will be a very important subject for the Assembly during my term as Speaker.

Problems deriving from the increasing number of Life Members have had a significant effect on APA. The seriousness of this phenomenon is even greater for some district branches, where expenses have increased while dues collection has not kept pace. The Constitutional and Assembly membership committees would do well to consider changing the "95" requirement (age plus years of membership) to something closer to 105 total years or 5 more years of dues payment. In the meantime, some district branches have raised money through voluntary contributions. This mechanism is recommended for district branches and the national APA while we develop long-term plans. Modification to address full retirement from practice, and possibly half-time practice, warrants evaluation for value and impact.

Other economic factors have led to the appointment of the Resource Development Committee, which will acquire funding for a number of emerging activities that require financial support. Such fund-raising could enable us to avoid large dues increases, which might otherwise become necessary.

Another APA strength has evolved: our importance in international affairs. Our voice and role have been highly recognized, to a large extent through the vigorous and tireless efforts of Ellen Mercer, Director of the Office of International Affairs. APA is seen as a leader in the field. We have identified and investigated problems of human rights in South America, and our role in the Soviet Union has been outstanding and effective. The continued activity of this APA office does us credit and calls for thanks to the Medical Director, Mel Sabshin, who introduced and nurtured this program.

The Joint Commission on Public Affairs, under the energetic leadership of Harvey Rubin and John Blamphin, has developed programs to reduce stigma in psychiatry. This is a product of President Paul Fink's earlier and continued activity. The next year holds promise of even greater results, since several films are being developed. John McGrath and Jay Cutler of the Joint Commission on Government Relations have been brilliant and have achieved outstanding accomplishments. Their role in effecting legislative changes and representing psychiatry to Congress has been highly productive in terms of budget and legislative initiatives, and their continued activity will be deeply appreciated. To assist this, I encourage all our members to join the Corporation for the Advancement of Psychiatry and support its Political Action Committee to help increase our impact on legislation.

We should also bear in mind the value of membership support of the research budgets for the Alcohol, Drug Abuse, and Mental Health Administration, the National Institute of Mental Health, and the National Institute on Drug Abuse, since all psychiatrists, clinical as well as academic, benefit as the scientific basis of our field is enriched and our therapeutic skills are enhanced.

In conclusion, I want to emphasize how fortunate and effective APA has been with the leadership of Paul Fink as President and Jack McIntyre as Speaker. I feel fortunate to have been able to work with Herb Pardes as President-Elect and look forward to working with him on the Board of Trustees in the coming year. Herb's appreciation and respect for the Assembly will show up in many ways, and his leadership and advancement of psychiatrists as scientists and practitioners will be valuable in further advancing the respectability of our discipline.

I cannot say enough about the fantastic job our Speaker, Jack McIntyre, has done in the past years. His wisdom, compassion, and twinkling sense of humor have been superb and effective in moving agendas, resolving conflicts, and replacing heat with light, passion with wisdom. His judgment on committees and task force appointments has been impeccable and further contributed to his and the Assembly's effectiveness. He is a very hard act to follow!

No Speaker-Elect report can be complete without full homage to the Central Office staff and leadership of APA. Mel Sabshin has assembled an outstanding staff, who have been very helpful to me in developing a perspective of the past. This helped me implement my role of Speaker-Elect in many facets of the job. Carolyn Robinowitz, as Mel's loyal deputy, has been an aid and often a facilitator. Corky Hart has been a valuable person in her role with the Joint Reference Committee. Lea Mesner's work with the Board of Trustees and as an Assembly back-up is much appreciated. Amy Conrick has been invaluable on Assembly business of all kinds. Alison Bondurant served with dedication in working with Herb Pardes and me on appointments to components. Jeanne Robb plays many roles—coordinator of the Board and Assembly, guide and institutional memory for area councils and the Assembly Executive Committee, and friend. Too easily overlooked because of the smoothness of operation is the Office of Meetings Management. George Campbell and Olga Damschen have made the meetings of the Assembly and the components and many other APA functions seem effortless and very comfortable for all of us through their very efficient and professional activity, and on behalf of all of us, I say, "Many thanks."

The members of the Assembly rate kudos that I should like to have been able to personalize for each of them and their regions. It has been a pleasure to visit the regions through the area councils and see how diligent, thoughtful, and committed to APA they are.

I appreciate the honor bestowed on me and will strive to justify their faith in electing me.

Report of the Committee on Constitution and By-Laws

Ralph O'Connell, M.D., Chairperson

The Committee on Constitution and By-Laws held one formal meeting this year. I wish to thank the members of the committee, Drs. Henry Payson and Richard Thurrell, our Assembly liaison Dr. Lee Park, and staff person Ms. Carol Lehmann for handling committee business expeditiously.

The committee discussed issues referred to it by the Board of Trustees from the Committee on Membership. At this time no resolution has been reached, but the committee plans to meet in September and will be conferring with the Committee on Membership and the Budget Committee.

On referral from the Board, the committee prepared an amendment to the by-laws that would allow the Speaker-Elect to vote at Board meetings when he or she attends in place of the Speaker.

Proposed Amendment to the By-Laws

The following amendment was approved by the Board of Trustees in March 1989 for reading to the membership at the 1989 annual meeting. It will be disseminated to the membership not later than Jan. 1, 1990, and will appear on the 1990 ballot. In the text below italics indicate additions:

Chapter Three. Board of Trustees

2. The voting members of the Board shall consist of the six Officers of the Association, its three immediate Past Presidents, the Speaker of the Assembly *(or the Speaker-Elect in the Speaker's absence),* three Trustees elected at large, a Member-in-Training Trustee elected at large, and one Trustee elected by the membership of each geographical area defined by the Assembly. A Member-in-Training Trustee Elect, elected at large, shall serve for a one-year term without a vote. Past Presidents, after serving a three-year term, shall continue as members of the Board without a vote.

Report of the Committee on Membership

Michael J. Vergare, M.D., Chairperson

The Committee on Membership met on Sept. 7, 1988, and Nov. 8–11, 1988, in Washington, D.C. Present were Drs. Michael J. Vergare (chairperson), Jack W. Bonner III, Fernando J. Cabrera, Lois E. Fuller, Robert L. Leon, Rodrigo A. Munoz, Donna M. Norris, Norman Rosenzweig, Aron S. Wolf (Assembly liaison), Jane C. Wells (consultant), and Office of Membership staff. The following guests were also present: Drs. Nada Stotland (chairperson, Committee on Women), Peggy Stephens (Committee on Women), Boris Rifkin (Committee on Private Practice), Melvin Sabshin (Medical Director), and Carolyn B. Robinowitz (Deputy Medical Director). The committee met jointly with the Assembly Committee on Recruitment/Retention and Membership Affairs on Friday, Nov. 11, 1988.

Membership Development

The committee reviewed extensive information on membership, noting the substantial growth achieved in the last decade, as well as different patterns of enrollments and losses among the APA areas and district branches. In the last decade alone, the APA membership has increased from 24,676 members in January 1979 to 35,168 at the beginning of 1989, for an average net gain of almost 1,050 members per year. As of March 1, 1989, the total membership was 35,373.

Of particular interest was the enrollment of Medical Student Members and Members-in-Training and the rate of retention as these younger members move through the educational/training process and advance to Members-in-Training and General Members, respectively. During 1984, the first year for the Medical Student class, APA enrolled 208 Medical Student members, who now number 676 and account for 2% of the total membership. The number of Members-in-Training has increased from 4,220 at the end of 1984 to 5,638 as of March 1, 1989. Members-in-Training account for 15.9% of the total membership of 35,373. The changes in membership from Jan. 1, 1983, to Jan. 1, 1989, can be seen in table 1.

Fewer than half of all district branches assess Medical Student dues. Areas with higher than average district branch student dues tend to have lower numbers of Medical Student members. Medical Students are becoming an important source of Members-in-Training: in 1987, 103 students advanced to Member-in-Training after enrolling in approved psychiatry residency training programs, and during 1988, 136 Medical Student members were upgraded to Members-in-Training.

During 1988, 1,159 Members-in-Training were enrolled and 922 Members-in-Training were advanced to General Member status, compared to 1,163 enrolled and 820 advanced in 1987. It is increasingly evident that Members-in-Training are fast becoming the greatest source of new General Members. While the number of all new General Members each year tends to be stable over time, the number of members who are first enrolled as General Members has decreased, while the proportion of those who become General Members by advancement has been growing steadily. Table 2 shows General Member enrollment versus advancement from Member-in-Training for the past 5 years. The committee believes that retention of younger members, therefore, deserves greater attention than ever before and urges APA and its district branches to consider increasing their efforts to meet the needs of young psychiatrists-in-training.

Membership transactions for all categories of membership during 1988 can be seen in table 3.

Eligibility of Osteopathic Physicians for General Membership

The committee reviewed a request that graduates from osteopathic psychiatric residency programs be allowed to hold General Member status. The current policy on General Membership eligibility is that the applicant must have completed a residency program in psychiatry accredited by the Residency Review Committee for Psychiatry of the Accreditation Council for Graduate Medical Education. The committee reaffirmed that completion of a psychiatric residency program approved by the American Osteopathic Association does not fulfill this requirement.

Transfer of District Branch Affiliation

There was lengthy discussion of the problems resulting from failure to implement transfers in a timely fashion, and it is strongly recommended that the transferring district branch contact the member about the transfer procedure after receipt of a roster, notice of address change, etc., from the Central Office. Many transfers are initiated by the Central Office in response to notifications from members, but a systematic follow-up by district branches would be most effective. It is also necessary that the district branches whose members have moved enforce the policy of termination of membership for failure to transfer after 1 year. District branches have been encouraged to process each transfer within 60 days of receipt of the member's complete application for transfer.

AMA Recruitment of Psychiatry Residents

APA collaborated with the AMA in its recruitment campaign aimed at approximately 3,000 APA Members-in-Training who were identified as not belonging to the AMA. These residents received a mailing from the AMA inviting them to join and including a letter from Drs. Paul Fink and Melvin Sabshin and appropriate AMA materials. This campaign and APA's contributions are expected to be publicized by AMA in *American Medical News* later this year and possibly at the 1989 AMA annual meeting in June. The AMA reports that as of Feb. 2, 1989, 106 residents had applied for AMA membership.

Membership/Fellowship Actions

The committee recommended and the Board subsequently approved the following.

Requests for exemption from dual membership requirement. The committee denied the requests from two members of the Southern California Psychiatric Society to be exempt from the dual APA/district branch membership requirement.

Requests for retroactive membership enrollment. The committee recommended deferral of the request from the Michigan District Branch that the membership of Lafayette Clinic–VA Medical Center residents be made retroactive to 1985.

Request for retroactive advancement. The committee recommended approval of the request for a member of the Genesee Valley District Branch that his advancement to General Member status be made retroactive because of a delay in processing. The district branch assumed responsibility for the delay and recommended this action.

Requests for review of eligibility for Associate Member status. The committee reviewed two applications for Associate Membership submitted by the Oregon Psychiatric Association and the Northern California Psychiatric Society and an application for advancement from Member-in-Training to Associate Member from the Southern California Psychiatric Society. The committee recommended denial of the new applications and the advancement on the basis that the individuals did not meet the criteria for membership.

The Orange County Psychiatric Society requested the committee's recommendation on the transfer application of an Associate Member who joined APA in 1975 through the Eastern Missouri Psychiatric Society. In 1988 the member requested transfer to the Orange County Psychiatric Society. The district branch council rejected the application for transfer on the grounds that this member does not seem to meet the criterion of training or experience in psychiatry. The committee recommended that the member's request for transfer be accepted, since the decision for membership eligibility was made in 1975 and must be honored. Any changes made to the current policy cannot be implemented retroactively.

Fellowship nominations. The committee received 249 nominations for Fellowship and reviewed 241; five requests for waiver of the 8-year General Membership requirement were denied, 2 requests for waiver of the 2-year waiting period for resubmission were denied, and one nomination was not reviewed for lack of sufficient supporting documentation.

Of the 241 nominations reviewed, 210 (87.1%) were recommended for approval by the Board of Trustees (see table 3). The committee recommended that 207 nominees for advancement from General Member to Fellow be approved, three nominees for advancement from Life Member to Life Fellow be approved, decisions on 30 nominees for advancement from General Member to Fellow be deferred, and the decision on one nominee for advancement from Life Member to Life Fellow be deferred.

Corresponding Members/Fellows and Members-at-Large. The committee reviewed applications for membership/advancement and recommended that 18 applications for Corresponding Membership be accepted, five nominations for advancement from Corresponding Member to Corresponding Fellow be approved, one nomination for advancement from Corresponding Member to Corresponding Fellow be deferred, two nominations for new Corresponding Fellow be approved, and three applications for Member-at-Large status be accepted.

Membership termination for APA dues arrears. In compliance with Section 2 (Forfeiture of APA Membership) of the *Operations Manual of the Board of Trustees*, the committee reviewed the list of members whose 1987 dues were in arrears and recommended that they be dropped from APA membership. It was further recommended that administrative reinstatement be authorized for those who returned to good standing by Jan. 31, 1989, and were also in good standing in their district branches.

Dues relief and Inactive status. At its November 1988 meeting, the committee reviewed requests for dues relief and/or transfer to Inactive status and recommended that 26 requests for special consideration be deferred pending receipt of district branches' recommendation, 80 dues waivers be approved, 39 dues waivers to allow achievement of Life status be approved, 12 dues waivers be denied, 79 requests for transfer to Permanent Inactive Membership be approved, one request for transfer to Permanent Inactive Membership be denied, nine requests for transfer to Temporary Inactive status be approved, two requests for transfer to Temporary Inactive status be denied, 16 requests for dues reduction be approved, two requests for dues reduction be denied, three requests for deferral of dues be approved, one request for refund of dues be approved, and one request for refund of dues be denied.

Medical Student Membership

In response to concerns expressed by district branches, the Committee on Membership and the Assembly Committee on Recruitment/Retention and Membership Affairs discussed administrative difficulties in processing membership transactions and alternatives for facilitating APA affiliation for medical students. High mobility after graduation from medical school places an administrative burden on district branches.

Consideration was given to allowing a one-time membership fee for medical students and removing the district branch affiliation requirement. Medical Student members would continue to receive the same benefits, and they would be encouraged by the district branches to attend meetings and participate in other activities organized at the local level. These specific changes were referred to the APA Budget Committee and the Committee on Constitution and By-Laws. The Committee on Membership noted the special nature of this category (no vote and no credit toward years of total active membership) and believes that Medical Student members whose membership is terminated for nonpayment of dues, etc., may form a negative impression of the Association.

The Assembly, at its November 1988 meeting, approved in principle the proposed modifications for facilitating Medical Students'

APA affiliation. The Board of Trustees approved referral of the recommendation to the Budget Committee and the Committee on Constitution and By-Laws.

Termination of Membership for Nonpayment of Dues

By virtue of the early billing for membership dues (September preceding the dues year), APA has allowed flexibility to members in their tax planning and a relatively long period before the termination of membership for nonpayment is implemented.

The committee noted that the early payment rate of national APA dues is relatively high, and it is also recognized that the remaining members may face a variety of issues preventing early payment, including relocation, financial problems, retirement and illness, and philosophical differences that may lead to a decision to resign. However, even better payment practices might be encouraged by modifying the present schedule of notification of dues, arrears, and termination of membership for nonpayment.

Late payment of dues results in cash flow problems for district branches, and it is detrimental to their ability to budget appropriately. For district branches that conduct their own billing, consideration of the following options might be useful: 1) early billing, similar to APA's schedule (3 months before the dues year), 2) reimbursement by district branches to area councils that do not penalize the district branches for members who fail to pay dues, 3) billing on the first of every month to ensure notification of newly enrolled members and members advanced to higher dues categories of their dues obligations, 4) dues policies that are conducive to membership retention—for example, not penalizing members for such district branch administrative errors as failure to send bills, 5) solicitation of voluntary contributions from dues-exempt members, and 6) other fund-raising activities.

The committee recommended the following, which the Budget Committee reviewed and approved at its Nov. 30, 1988, meeting.

1. Members will be encouraged to pay their dues for the current year no later than the time of the annual meeting in that year.
2. The schedule for termination of membership for nonpayment will be accelerated by 6 months. For example, the schedule for the 1990 dues year would be as follows: September 1989, first billing; January 1990, expected payment of dues; June 30, 1990, unpaid 1990 dues considered in arrears; June 30, 1991, membership terminated for nonpayment (in keeping with the 1-year constitutional requirement) (December 1991 under previous policy).
3. This change will be accompanied by a strong publicity campaign with maximum advance notice of the change. The publicity should stress the advantages of early payment to APA and the district branches and should state clearly the date when dues are considered to be in arrears, the actions that late payment precipitates, and the options available for hardship cases.

Care should be taken to support the intent of the Board of Trustees when it instituted the early billing practice, which was to increase members' options for scheduling payment of APA dues.

4. Provisions will be made to ensure that the change does not adversely affect members who enroll or are advanced close to the end of the membership year or adversely affect members approaching Life Status.
5. This modification will be implemented for the 1990 dues year.
6. The modification will provide a one-time amnesty to former members who wish to rejoin and will forgive APA and district branch dues that are in excess of 1 year's debt.
7. This modification will be tried for a 2-year period and if judged successful, will be continued.

This recommendation was endorsed by the Assembly at its November 1988 meeting and was subsequently approved by the Board of Trustees.

Members-at-Large in Mexico, Central America, and the Caribbean

The committee, with the concurrence of the Assembly Committee on Recruitment/Retention and Membership Affairs and the Committee on Constitution and By-Laws, is recommending that Members-at-Large in Mexico, Central America, and the Caribbean (except Puerto Rico) be given the option of remaining in that category or transferring to Corresponding Member/Fellow status.

The reason for this alternative is the lack of a district branch structure in these areas; it is a means to facilitate affiliation with APA. For example, fewer than 30 psychiatrists in Mexico are currently APA Members-at-Large (dues-paying members with voting privileges), and it is felt that the option of joining as Corresponding Members (dues-exempt, publications by subscription only, nonvoting) would encourage more psychiatrists in that country to seek APA membership. The Board of Trustees approved the recommendation and referred the issue to the Committee on Constitution and By-Laws for implementation of necessary changes to the Constitution.

Members-at-Large/Corresponding Members Who Move Into District Branch Jurisdictions

The Committee on Membership reviewed the difficulties experienced at both the national and local levels in enforcing compliance with the dual membership requirement with respect to a Member-at-Large outside the United States or a Corresponding Member who moves into the jurisdiction of a district branch and fails to join. As there was no specific policy in the *Operations Manual* with respect to termination of membership, to facilitate compliance with the dual membership requirement the committee recommended that members who fail to apply for district branch membership within a year be dropped from APA membership. The Board of Trustees approved this recommendation.

Associate Membership

Concerns have been expressed about the category of Associate Member and the criteria for eligibility (1 year of acceptable full-time training or experience in psychiatry). Both membership committees discussed the problems resulting from claims by those with marginal credentials in the profession that they are fully practicing psychiatrists by virtue of their APA membership. Further review of the criteria for other categories, such as Honorary and Distinguished Fellow, indicated that these criteria may be sufficient to accommodate prominent physicians who have made significant contributions to psychiatry. Therefore, both membership committees recommended that no new applicants for Associate Membership be approved. The Board of Trustees deferred action on this recommendation pending a full report from the Committee on Membership on the history of Associate Membership. Pending the full report, the Board of Trustees approved the recommendation that no new applicants for this category be accepted and that any current members with this status be permitted to retain it.

Eligibility of Primary Care Residents for Member-in-Training Status

Residents have the option of entering either 1) a 1-year primary care training program (such as family medicine or pediatrics) that is followed by a 3-year psychiatry residency or 2) a 4-year psychiatry program in which the primary care experience is built into the program. The policy in the *Operations Manual* states, "Members-in-Training are physicians who have been accepted into a psychiatric residency training program that is approved by the Residency Review Committee for Psychiatry of the Accreditation Council for Graduate Medical Education or Royal College of Physicians and Surgeons of Canada, and remain enrolled therein. . . ." The committee recommended a change to the *Operations Manual* to indicate that residents enrolled in a 1-year primary care training program that precedes a 3-year psychiatry residency are eligible for the Member-in-Training category. The Board approved this recommendation.

Licensure Requirements

At its December 1987 meeting, the Board of Trustees requested that the Committee on Membership clarify the circumstances in which a valid medical license is not a prerequisite for continued membership. In addition to the exemptions from the licensure requirement currently included in the Constitution and By-Laws (By-Laws Chapter One: "an academic, research, or governmental position that does not require licensure"), the committee recommended that fully retired members be exempt from the need to hold a valid medical license. The Board of Trustees approved the recommendation that the *Operations Manual* be revised to reflect this exemption.

Report of the Committee of Tellers

Edward Kirby, M.D., Chairperson

The Committee of Tellers met on April 4, 1989, at APA headquarters to certify the results of the 1989 election. Ballots were mailed on Feb. 16, 1989, to 32,790 eligible voting members; 92 undeliverable ballots were deducted from that number, so the adjusted number of eligible voting members was 32,698. Included in the final tally were the 15,518 ballots that were returned (47.5% of the eligible voting members).

The Committee of Tellers acted on uncertain votes, which had been held for its decisions. It also ascertained that all candidates had verified the accuracy of their biographical statements and had submitted the required statements of compliance with election guidelines.

The Committee of Tellers certified that the following were elected to office and so reported to the Board of Trustees—President-Elect: Elissa P. Benedek, M.D. (50.8% of the votes cast), Vice-President: Fred Gottlieb, M.D. (60.6%), Secretary: Philip M. Margolis, M.D. (50.5%), Trustee-at-Large: Roger Peele, M.D. (51.0%), Member-in-Training Trustee-Elect: Eliza W. Menninger, M.D. (55.8%), Area III Trustee: Chester W. Schmidt, M.D. (52.0%), and Area VI Trustee: Daniel B. Borenstein, M.D. (60.1% of votes cast).

The Committee of Tellers recommended that the Board of Trustees accept the results of the 1989 election, and the Board accepted them.

Guidelines Regarding Psychiatrists' Signatures

These guidelines were prepared by the Council on Psychiatric Services[1] and were approved by the Board of Trustees on June 25, 1989.

The signature of a physician represents the formal statement that places the physician in a legally and ethically responsible status for the action or consequences of the signed document. The supervision or leadership by psychiatrists of other professionals or trainers of other disciplines is also acknowledged by the American Psychiatric Association as a legitimate process for third-party reimbursement for treatment of mental illness (supervision is defined in the APA "Guidelines for Relationships of Psychiatrists With Nonpsychiatrist Professionals"). A psychiatrist should be guided by the following guidelines for signing documents:

1. The signature of a psychiatrist on a diagnostic formulation or treatment plan signifies that the psychiatrist reviewed it, agreed with the diagnosis, and approved of the plan. This does not necessarily signify that he or she has seen the patient or carried out the evaluation. It may imply only that he or she is head or a member of a multidisciplinary team or supervisor of other professionals or trainees.

The psychiatrist should clarify his or her role in the process of the formulation by writing immediately before his or her signature "Reviewed by [name]" or "Under the supervision of [name]" or "Team Leader Approval" or other clarification.

2. The initiation of pharmacological treatment by a psychiatrist will require the direct evaluation of the patient. This should include a comprehensive review of relevant history—medical history, psychiatric history, and previous response to medication. There may be circumstances where a direct evaluation is not possible at the time of prescription or order. In this case, evaluation should be completed in a timely fashion. Maintenance of medication regimens also requires periodic direct reevaluation of the patient.

3. The signature of a psychiatrist on an insurance or other third-party form for billing purposes signifies that the patient has received the treatment for which the third party is being billed. Wording on the form must be carefully scrutinized to ensure that the information is accurate. The psychiatrist is obligated to correct any errors or misconceptions since he or she will be held responsible. The psychiatrist should make clear on the form precisely the services that he or she is claiming and whether and to what extent he or she has directly treated or evaluated the patient. This obligation may be met by writing in before the signature a phrase such as "Under the supervision of [name]" or "Reviewed by [name]" or "Approved by [name]." The psychiatrist may also review the patient's record or require additional information to ensure that the diagnosis is accurate and the services being billed for have been documented.

4. The signature of a psychiatrist for quality assurance, peer review, or other administrative review should indicate on the form that the evaluation was based on review of [specify what was reviewed] and an approximate length of time of the review.

---

[1] The council includes J. Frank James, M.D. (chairperson), Bert Pepper, M.D. (vice-chairperson), Harvey D. Strassman, M.D., Naomi Goldstein, M.D., Sheila B. Blume, M.D., Rena Magno Nora, M.D. (observer-consultant), William L. Webb, Jr., M.D. (Board liaison), Chester W. Schmidt, Jr., M.D. (Board liaison), Albert C. Gaw, M.D. (Assembly liaison), Seymour Gers, M.D. (Assembly liaison), and Julia A. Matthews-Bellinger, M.D. (APA/Burroughs Wellcome Fellow); David J.M. Whitehouse, M.D., provided consultation as a representative of the Ethics Committee.

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Contraindications: Comatose states or presence of large amounts of C.N.S. depressants.

Warnings: The possibility of extrapyramidal reactions from chlorpromazine may confuse the diagnosis of Reye's syndrome or other encephalopathy. Therefore, avoid use in children or adolescents with suspected Reye's syndrome.

May cause persistent tardive dyskinesia, which appears to be irreversible in some patients. Reserve chronic neuroleptic treatment for patients with chronic illness 1) that is known to respond to neuroleptics and 2) for whom there are no safer but equally effective treatment options. Use the smallest effective dose over the shortest treatment duration. If signs and symptoms of tardive dyskinesia develop, consider discontinuing the neuroleptic. A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. To manage NMS 1) discontinue immediately antipsychotic drugs and any other drugs not essential to concurrent therapy; 2) treat symptoms intensively and monitor; 3) where possible, treat serious concomitant medical problems. If antipsychotic treatment is needed after recovery from NMS, consider reintroducing drug therapy and monitor the patient carefully as recurrences of NMS have been reported. 'Thorazine' ampuls and vials contain sodium bisulfite and sodium sulfite; the sulfite may cause allergic reactions, including anaphylactic symptoms. In patients with bone marrow depression or previously demonstrated hypersensitivity (e.g., blood dyscrasias, jaundice) with phenothiazines, do not administer 'Thorazine' unless the potential treatment benefits outweigh the possible hazards. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days therapy. Avoid concomitant use with alcohol. May counteract antihypertensive effect of guanethidine and related compounds. Use in pregnancy only when essential. There are reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborns whose mothers had received chlorpromazine. Chlorpromazine is excreted in the breast milk of nursing mothers.

Precautions: Advise patients and/or guardians of the risk of tardive dyskinesia from chronic therapy. Use cautiously in persons with cardiovascular, liver or chronic respiratory disease, or with acute respiratory infections. Patients with a history of hepatic encephalopathy due to cirrhosis have increased sensitivity to the C.N.S. effects of chlorpromazine. Due to cough reflex suppression, aspiration of vomitus is possible. May prolong or intensify the action of C.N.S. depressants, organophosphorus insecticides, heat, atropine and related drugs. (Reduce dosage of concomitant C.N.S. depressants.) Anticonvulsant action of barbiturates is not intensified.

Neuroleptic drugs cause elevated prolactin levels that persist during chronic administration. Since approximately one-third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug administration is contemplated in a patient with a previously detected breast cancer. Neither clinical nor epidemiologic studies to date, however, have shown an association between the chronic administration of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in glaucoma patients. May diminish the effect of oral anticoagulants, produce α-adrenergic blockade, and lower the convulsive threshold; dosage adjustment of anticonvulsants may be required. May interfere with Dilantin®* metabolism, causing 'Dilantin' toxicity. May cause false positive phenylketonuria test results. Do not use with Amipaque®†. Discontinue 'Thorazine' at least 48 hours before myelography, do not resume for at least 24 hours postprocedure, and do not use to control N/V prior to myelography or postprocedure with 'Amipaque'. Evaluate patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics periodically to decide whether the dosage could be reduced or therapy discontinued. Antiemetic effect may mask signs of overdosage of other drugs or obscure diagnosis and treatment of conditions such as intestinal obstruction, brain tumor and Reye's syndrome (see Warnings). When used concomitantly, may obscure vomiting as a sign of toxicity of a cancer chemotherapeutic agent. Discontinue high-dose, long-term therapy gradually. Patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics should be evaluated periodically for possible adjustment or discontinuance of drug therapy.

Adverse Reactions: Drowsiness; cholestatic jaundice; agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, aplastic anemia, thrombocytopenic purpura and pancytopenia; postural hypotension, tachycardia, fainting, dizziness and occasionally a shock-like condition; reversal of epinephrine effects; EKG changes have been reported; neuromuscular (extrapyramidal) reactions: dystonias, motor restlessness, pseudo-parkinsonism, persistent tardive dyskinesia, psychotic symptoms, catatonic-like states, cerebral edema; convulsive seizures; abnormality of the cerebrospinal fluid proteins; urticarial reactions and photosensitivity, exfoliative dermatitis, contact dermatitis; asthma, laryngeal edema, angioneurotic edema, and anaphylactoid reactions; lactation and breast engorgement (in females on large doses), false positive pregnancy tests, amenorrhea, gynecomastia; hyperglycemia, hypoglycemia, glycosuria; dry mouth, nasal congestion, constipation, adynamic ileus, urinary retention, priapism, miosis, mydriasis; after prolonged substantial doses, skin pigmentation, epithelial keratopathy, lenticular and corneal deposits and pigmentary retinopathy, visual impairment; mild fever (after large I.M. doses); hyperpyrexia; increased appetite and weight; a systemic lupus erythematosus-like syndrome; peripheral edema.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported but no causal relationship has been established.

How Supplied: Tablets: 10 mg., 25 mg. or 50 mg., in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 100 mg. and 200 mg., in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only).

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THE BRITISH JOURNAL OF PSYCHIATRY

AUGUST 1989 VOLUME 155

Review Article

The role of electroconvulsive therapy in the treatment of depressive illness in old age. *S.M. Benbow* 147

Papers

French empirical criteria for the diagnosis of non-affective non-organic psychoses: comparison between the criteria suggested by Professors Pull and Pichot and those of DSM-III-R. *A.M.P. Kellam* 153

The delineation of schizophrenia from other psychiatric illnesses. *E. Ph. Kazanetz* 160

Slowly progressive schizophrenia—myth or clinical reality? *A.B. Smulevitch* 166

The factor structure of the General Health Questionnaire (GHQ–30): a reliability study on 6317 community residents. *F.A. Huppert, D.E. Walters, N.E. Day and B.J. Elliott* 178

Chronic psychiatric complaints and the General Health Questionnaire. *M.W.J. Koeter, W. van den Brink and J. Ormel* 186

Differential classification in school refusal. *L. Atkinson, B. Quarrington, J.J. Cyr and F.V. Atkinson* 191

Distorting patient or distorting instrument? Body shape disturbance in patients with anorexia nervosa and bulimia. *P.K. Bowden, S.W. Touyz, P.J. Rodriguez, R. Hensley and P.J.V. Beumont* 196

Major depression in Down's syndrome. *A.C. Warren, S. Holroyd and M.F. Folstein* 202

Wilson's disease: a prospective study of psychopathology in 31 cases. *T.R. Dening and G.E. Berrios* 206

An epidemiological study of dementia in a rural population of elderly women. *C. Brayne and P. Calloway* 214

Mania in the elderly. *K. Stone* 220

Schizophrenia and the perception of emotions: how accurately do schizophrenics judge the emotional states of others? *P. Cramer, M. Weegmann and M. O'Neil* 225

The contribution of problem drinking to the level of psychiatric morbidity in the general hospital. *M.A. Schofield* 229

Resettlement of old long-stay psychiatric patients: the use of the private sector. *R.E. Perkins, S.A. King and J.A. Hollyman* 233

Signal and noise in psychiatry: the role and control of non-specific factors. *H. Omer and P. London* 239

Brief Reports

Epilepsy and violence. *C.G. Hindler* 246

Pimozide in pathological jealousy. *A. Byrne and L.N. Yatham* 249

A Chinese classic phenylketonuria manifested as autism. *C.S. Chen and K.J. Hsiao* 251

Depression-dependent exacerbation of tardive dyskinesia. *P.S. Sachdev* 253

A case of doll phobia. *S. Hatcher* 255

'Puerperal psychosis' following male-to-female sex reassignment? *P. Mallett, E.J. Marshall and C.V.R. Blacker* 257

Syphilis serology screening in a psychogeriatric population: is the effort worthwhile? *J.A. Boodhoo* 259

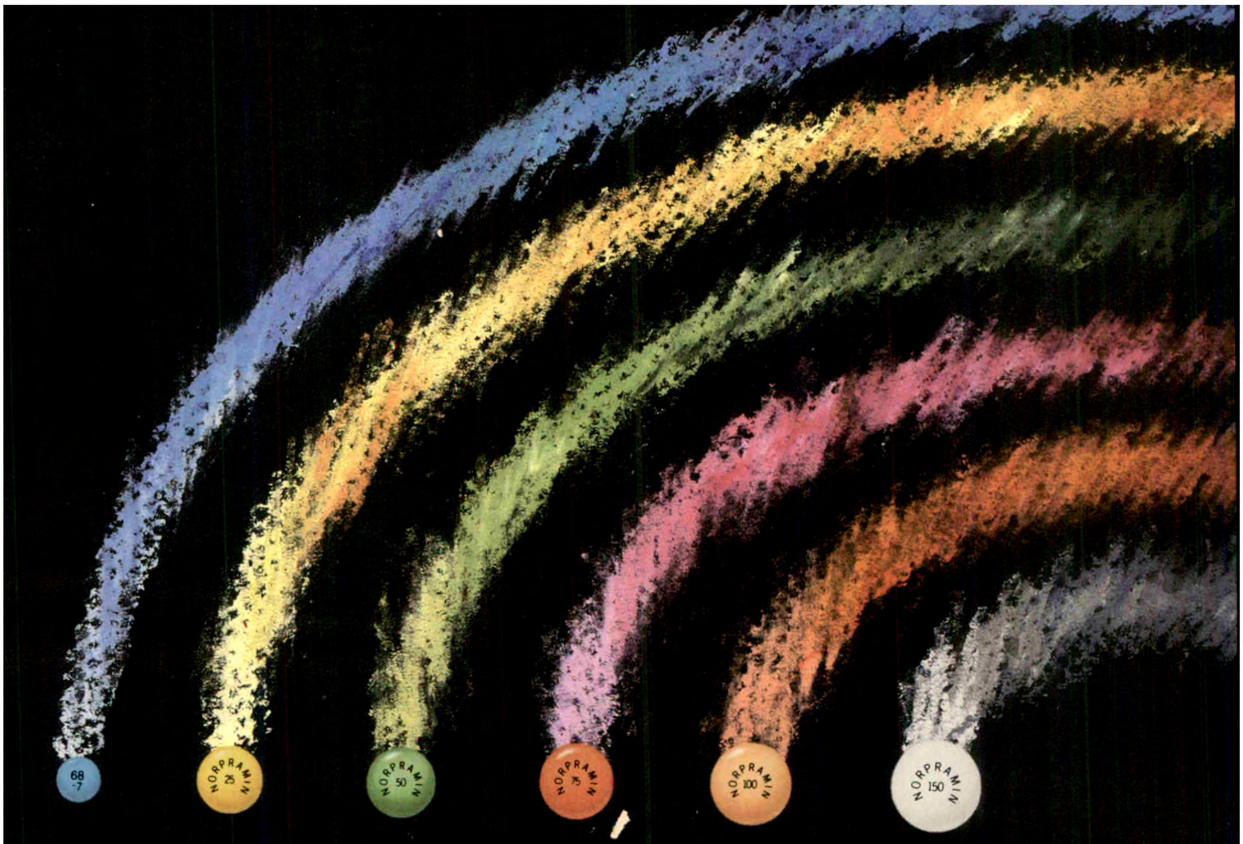
Correspondence 263

A hundred years ago. *Researched by Henry Rollin* 270

Books Reconsidered

Psychopathic Personalities (Kurt Schneider). *K. Standage*

Book Reviews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CLINICAL PHARMACOLOGY

Metabolism

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Additional information on metabolism appears in Full Prescribing Information.

CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS

1. Extreme caution should be used when this drug is given in the following situations:
   a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
   b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
   c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
   d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
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   Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
4. **USE IN CHILDREN**
   Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. (See ADVERSE REACTIONS, Cardiovascular.)
5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

PRECAUTIONS

1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
2. If serious adverse effects occur, dosage should be reduced or treatment should be altered.
3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
4. The drug may cause exacerbation of psychosis in schizophrenic patients.
5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
9. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
10. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
11. Both elevation and lowering of blood sugar levels have been reported.
12. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

ADVERSE REACTIONS

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. There has been a report of an "acute collapse" and "sudden death" in an eight-year old (18 kg) male, treated for two years for hyperactivity. (See WARNINGS, Use in Children.)

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

OVERDOSAGE

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotension, shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts of early evacuation of the ingested material and subsequent support of respiration (airway and movement), circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are well known in most medical centers and are not further discussed here.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be given. Because of the short duration of action of physostigmine, the effective dose should be repeated at 30-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

(a) Dialysis: Desipramine is found in low concentration in the serum, even after a massive oral dose. In vitro experiments in which blood bank blood was used indicate that it is very poorly dialyzed. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.

(b) Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopressor agents as levarterenol and metaraminol, they should be used only with caution.

(c) Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice for the control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenylhydantoin, which has less central depressant effect but also has an effect on heart rhythm that has not yet been fully defined.

(d) Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravascular volume must be maintained by i.v. fluids. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

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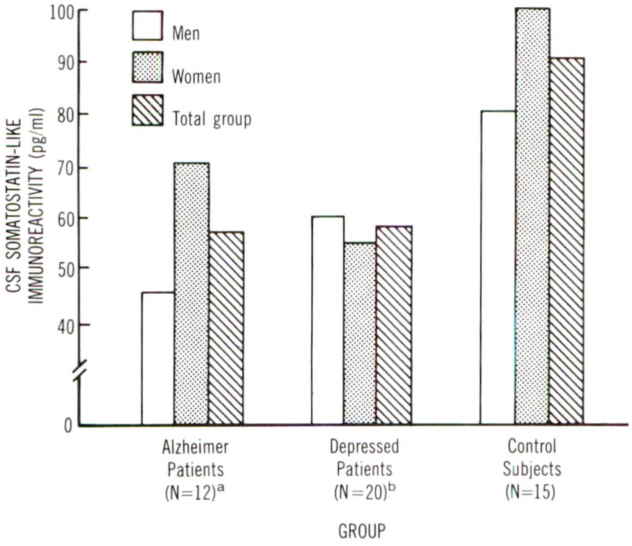

[a] Significant difference between men and women ($t=1.81$, $df=10$, $p<0.05$) and between the total Alzheimer's disease group and the total control group ($t=2.49$, $df=25$, $p<0.01$).

[b] Significant difference between the total depressed group and the total control group ($t=2.75$, $df=33$, $p<0.005$).

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Psychological Medicine

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EDITORIALS

Estimated costs of neurotic disorder in UK general practice 1985 C. CROFT-JEFFREYS AND G. WILKINSON 549

Schizophrenia and violence J. VOLAVKA AND M. KRAKOWSKI 559

How do the neuropathological changes of schizophrenia relate to pre-existing neurotransmitter and aetiological hypotheses? R.W. KERWIN 563

ORIGINAL ARTICLES

NEUGEBAUER, R. A doctor's dilemma: the case of William Harvey's mentally retarded nephew 569

PEARLSON, G.D., RABINS, P.V., KIM, W.S., SPEEDIE, L.J., MOBERG, P.J., BURNS, A. AND BASCOM. M.J. Structural brain CT changes and cognitive deficits in elderly depressives with and without reversible dementia ('pseudodementia') 573

WINTON, F., CORN, T., HUSON, L.W., FRANEY, C., ARENDT, J. AND CHECKLEY, S.A. Effects of light treatment upon mood and melatonin in patients with seasonal affective disorder 585

ELPHICK, M. Clinical issues in the use of carbamazepine in psychiatry: a review 591

KOPONEN, H., STENBÄCK, U., MATTILA, E., REINIKAINEN, K., SOININEN, H. AND RIEKKINEN, P.J. Cerebrospinal fluid somatostatin in delirium 605

ROBERTSON, M.M., TRIMBLE, M.R. AND LEES, A.J. Self-injurious behaviour and the Gilles de la Tourette syndrome: a clinical study and review of the literature 611

FORD, R.A. The psychopathology of echophenomena 627

DEAN, C., WILLIAMS, R.J. AND BROCKINGTON, I.F. Is puerperal psychosis the same as bipolar manic-depressive disorder? A family study 637

BIRCHWOOD, M., SMITH, J., MACMILLAN, F., HOGG, B., PRASAD, R., HARVEY, C. AND BERING, S. Predicting relapse in schizophrenia: the development and implementation of an early signs monitoring system using patients and families as observers, a preliminary investigation. 649

PANTELIS, C., HINDLER, C.G. AND TAYLOR, J.C. Use and abuse of khat (*Catha edulis*): a review of the distribution, pharmacology, side effects and a description of psychosis attributed to khat chewing 657

BASS, C., LELLIOTT, P. AND MARKS, I. Fear talk *versus* voluntary hyperventilation in agoraphobics and normals: a controlled study 669

DEADMAN, J.M., DEWEY, M.J., OWENS, R.G., LEINSTER, S.J. AND SLADE, P.D. Threat and loss in breast cancer 677

HARRISON, G., HOLTON, A., NEILSON, D., OWENS, D., BOOT, D. AND COOPER, J. Severe mental disorder in Afro-Caribbean patients: some social, demographic and service factors 683

CHENG, T.A. Symptomatology of minor psychiatric morbidity: a cross cultural comparison 697

GALLACHER, J.E.J. AND SMITH, G.D. A framework for the adaptation of psychological questionnaires for epidemiological use: an example of the Bortner Type A scale 709

GATER, R.A., DEAN, C. AND MORRIS, J. The contribution of childbearing to the sex difference in first admission rates for affective psychosis 719

MACCARTHY, B., LESAGE, A., BREWIN, C.R., BRUGHA, T.S., MANGEN, S. AND WING, J.K. Needs for care among the relatives of long-term users of day care. A report from the Camberwell High Contact Survey 725

SCHWARTZ, S. AND LINK, B.G. The 'well control' artefact in case/control studies of specific psychiatric disorders 737

MORGAN, D. Psychiatric cases: an ethnography of the referral process 743

WILMINK, F.W. AND SNIJDÉRS, T.A.B. Polytomous logistic regression analysis of the General Health Questionnaire and the Present State Examination 755

TANSELLA, M. AND WILLIAMS, P. The spectrum of psychiatric morbidity in a defined geographical area 765

O'CONNOR, D.W., POLLITT, P.A., TREASURE, F.P., BROOK, C.P.B. AND REISS, B.B. The influence of education, social class and sex on Mini-Mental State scores 771

FOMBONNE, E. The Child Behaviour Checklist and the Rutter Parental Questionnaire: a comparison between two screening instruments 777

RESEARCH REPORT

The General Practice Research Unit at the Institute of Psychiatry G. WILKINSON 787

BOOK REVIEWS

The Scope of Epidemiological Psychiatry B. BURNS 791

Neuroendocrinology of Mood B. DONOVAN 792

Sentenced to Hospital: Offenders in Broadmoor P. BOWDEN 794

Neural Networks and Natural Intelligence G.S. BRINDLEY 795

Psychopharmacology and Reaction Time A. PARROTT 795

SHORT REVIEWS 797

PSYCHIATRY IN THE 1880s 805

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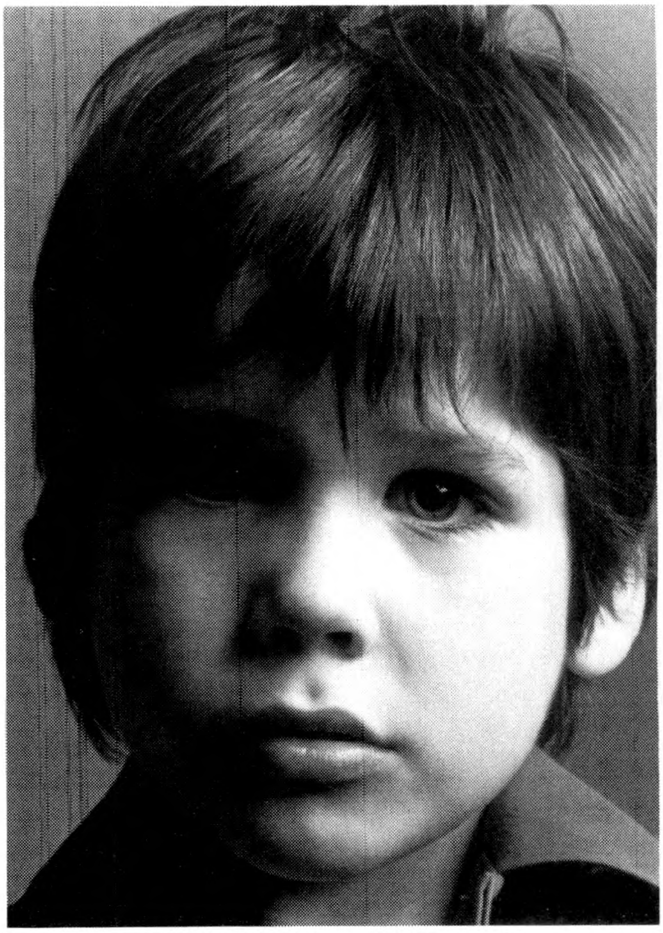

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BURROUGHS WELLCOME CO.
  Wellbutrin A17–A24

CADWELL LABORATORIES A11

CIBA-GEIGY PHARMACEUTICALS
  Treatment IND A15

DISTA PRODUCTS/DIV. OF ELI LILLY & CO.
  Prozac A36–A38

DORSEY DIVISION/SANDOZ PHARMACEUTICALS
  Mellaril A40
  Pamelor A13

EMPLOYMENT OPPORTUNITIES A52–A54

HOSPITAL CORP. OF AMERICA A39

LEDERLE LABORATORIES
  Asendin A27–A28

LEMMON COMPANY
  Orap A29–A30

MCNEIL PHARMACEUTICAL
  Haldol Decanoate C3–C4

MEAD JOHNSON PHARMACEUTICAL
  Buspar C2–A1
  Desyrel A2

MECTA CORPORATION A26

MEETINGS & SYMPOSIA A35, A52

PDLA A2

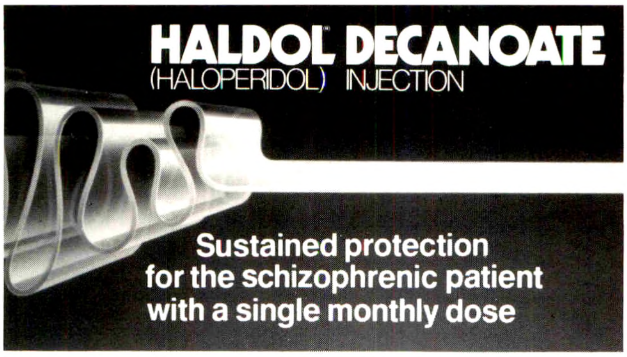
PLENUM PUBLISHING A26

ROCHE LABORATORIES
  Valium A33–A35

ROERIG DIV./PFIZER, INC.
  Navane A6–A8
  Sinequan A31–A32

SMITH, KLINE, FRENCH LABS
  Stelazine A25–A26
  Thorazine A41–A42

THOMAS, CHARLES C., PUBLISHERS A43



The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia*—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

7/20/88

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THE 5 mL MULTI-DOSE VIAL

- ☐ same 50 mg/mL concentration
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Sustained drug levels with a single monthly dose

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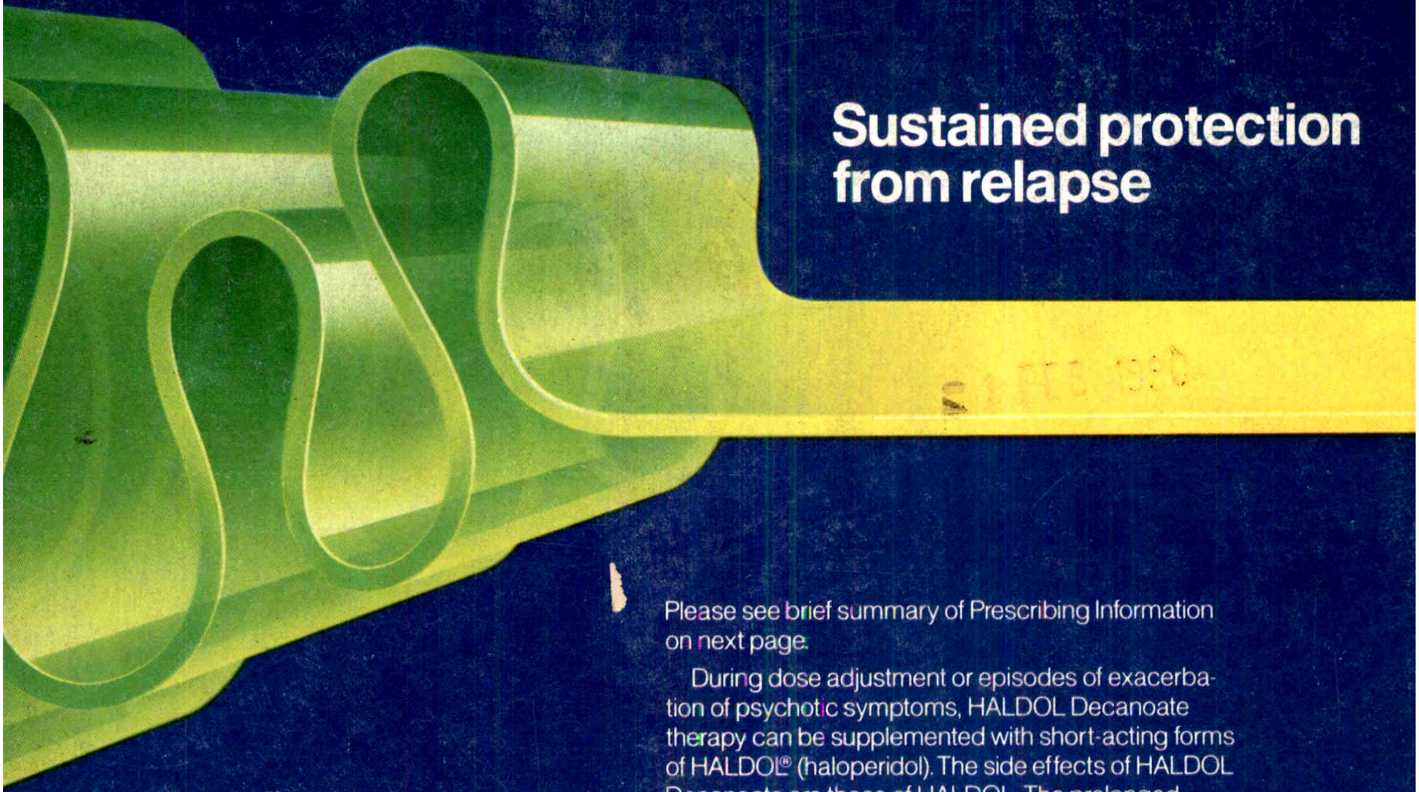

Sustained protection from relapse

21 FEB 1990

Please see brief summary of Prescribing Information on next page.

During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL® (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.

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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 146, Number 11 November 1989

In this issue:

Fifty Years After Freud: Dora, the Rat Man, and the Wolf-Man
By Peter Buckley

A Developmental Perspective on Psychotherapy and Psychoanalysis
By Paul C. Holinger

Psychiatric Syndromes Linked to Reproductive Function in Women:
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Official Journal of the American Psychiatric Association

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- Brand necessary
- May not substitute
- No substitution
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Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety dis
symptoms of anxiety or anxiety associated with depre
tension associated with stress of everyday life usually
with an anxiolytic.
Effectiveness in long-term use, i.e., more than 4 mo
by systematic clinical studies. Reassess periodically
individual patient.

Contraindications: Known sensitivity to benzodiaze
glaucoma.

Warnings: Not recommended in primary depressive
As with all CNS-acting drugs, warn patients not to ope
vehicles, and of diminished tolerance for alcohol and
Physical and Psychological Dependence: Withdrav
noted with barbiturates and alcohol have occurred fol
ance of benzodiazepines (including convulsions, tren
cramps, vomiting and sweating). Addiction-prone indi
and alcoholics, should be under careful surveillance v
because of their predisposition to habituation and dep
symptoms have also been reported following abrupt c
diazepines taken continuously at therapeutic levels fo

Precautions: In depression accompanying anxiety, c
suicide.
For elderly or debilitated patients, initial daily dosag
avoid oversedation. Terminate dosage gradually since
antianxiety agent may result in symptoms like those be
tion, irritability, tension, insomnia and occasional conv
precautions with impaired renal or hepatic function. W
diovascular disorders coexist with anxiety, note that lo
shown of significant benefit in treating gastrointestinal
nent. Esophageal dilation occurred in rats treated with
1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/
mum human therapeutic dose of 10mg/day). Effect wa
ment was withdrawn within 2 months of first observatic
unknown; but use of lorazepam for prolonged periods
caution and frequent monitoring for symptoms of uppe
effectiveness in children under 12 years have not beer

ESSENTIAL LABORATORY TESTS: Some patients hav
some have had elevations of LDH. As with other benzc
counts and liver function tests are recommended durir

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: B
CNS depressant effects when administered with such
or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidenc
emerged in rats during an 18-month study. No studies
have been performed.

PREGNANCY: Reproductive studies were performed i
rabbits. Occasional anomalies (reduction of tarsals, tit
limbs, gastroschisis, malformed skull and microphthal
treated rabbits without relationship to dosage. Althoug
not present in the concurrent control group, they have l
randomly in historical controls. At 40mg/kg and highe
resorption and increased fetal loss in rabbits which wa
Clinical significance of these findings is not known. Ho
congenital malformations associated with use of mino
poxide, diazepam and meprobamate) during first trim
been suggested in several studies. Because use of th
of urgency, use of lorazepam during this period shoulc
Possibility that a woman of child-bearing potential may
therapy should be considered. Advise patients if they l
municate with their physician about desirability of disc
humans, blood levels from umbilical cord blood indica
lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam
like other benzodiazepines. As a general rule, nursing
while on a drug since many drugs are excreted in milk

Adverse Reactions, if they occur, are usually observe
and generally disappear on continued medication or c
sample of about 3,500 anxious patients, most frequent
tion (15.9%), followed by dizziness (6.9%), weakness (
(3.4%). Less frequent are disorientation, depression, n
headache, sleep disturbance, agitation, dermatologic
disturbance, various gastrointestinal symptoms and au
Incidence of sedation and unsteadiness increased wit
blood pressure have been noted but are not clinically s
related to relief of anxiety.
Transient amnesia or memory impairment has been
the use of benzodiazepines.

Overdosage: In management of overdosage with any
agents may have been taken. Manifestations of overdc
confusion and coma. Induce vomiting and/or undertak
general supportive care, monitoring vital signs and clo
sion, though unlikely, usually may be controlled with Le
Injection U.S.P. Usefulness of dialysis has not been de

®

**DOSAGE: Individualize for maximum be
dose gradually when needed, giving
before increasing daytime doses.
day given b.i.d. or t.i.d.; dosage m
day in divided doses. For elderly c
1-2mg/day; insomnia due to anxie
stress, 2-4mg h.s.**

HOW SUPPLIED: 0.5, 1.0 and 2.0m

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Philadelphia, PA 19101

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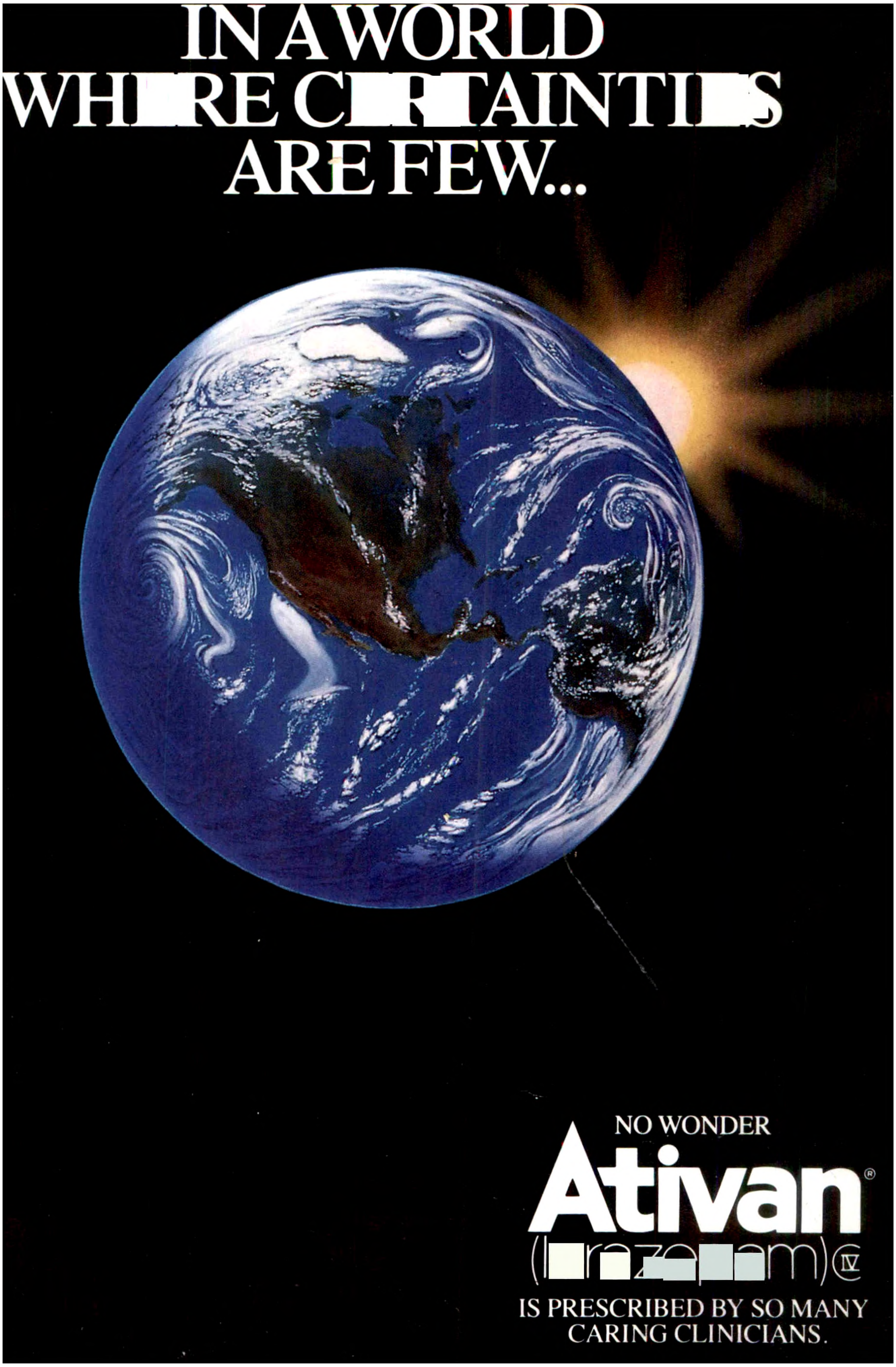
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IS PRESCRIBED BY SO MANY
CARING CLINICIANS.

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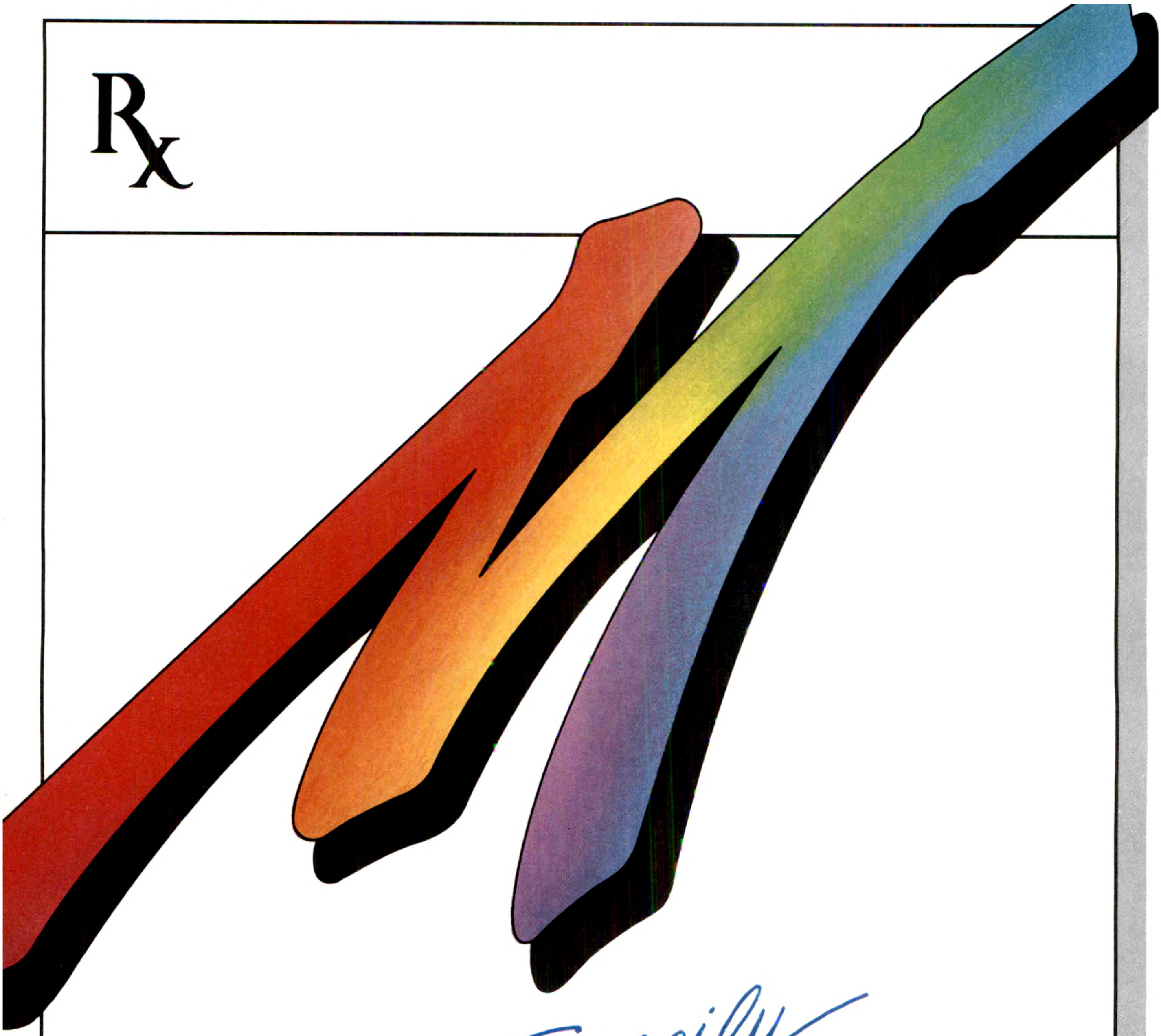

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(thioridazine)

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78-8
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MELLARIL 100
MELLARIL 150
MELLARIL 200

10 mg 15 mg 25 mg 50 mg 100 mg 150 mg 200 mg

MELLARIL
MELLARIL-S
25
100

30 mg/ ml 100 mg/ ml 25 mg/ 5 ml 100 mg/ 5 ml

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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 146, Number 11 November 1989

EDITORIAL

1391 ECT for Parkinson's Disease *Richard Abrams*

SPECIAL ARTICLES

1394 Fifty Years After Freud: Dora, the Rat Man, and the Wolf-Man *Peter Buckley*

1404 A Developmental Perspective on Psychotherapy and Psychoanalysis *Paul C. Holinger*

1413 Psychiatric Syndromes Linked to Reproductive Function in Women: A Review of Current Knowledge *Michael J. Gitlin and Robert O. Pasnau*

REGULAR ARTICLES

1423 Use of Medication and In Vivo Exposure in Volunteers for Panic Disorder Research *C. Barr Taylor, Roy King, Jürgen Margraf, Anke Ehlers, Michael Telch, Walton T. Roth, and W.S. Agras*

1427 Apparent Phase Advance in Diurnal MHPG Rhythm in Depression *Harry E. Gwirtsman, Angelos E. Halaris, Abraham W. Wolf, Edward DeMet, John E. Piletz, and Matthew Marler*

1434 Interhemispheric Transfer Deficit and Alexithymia *Sharon B. Zeitlin, Richard D. Lane, Daniel S. O'Leary, and Michael J. Schrift*

1440 Chronic Medical Conditions in a Sample of the General Population With Anxiety, Affective, and Substance Use Disorders *Kenneth B. Wells, Jacqueline M. Golding, and M. Audrey Burnam*

1447 A Reliability Assessment of the Psychotherapy Supervisory Inventory *Stephen B. Shanfield, Paul C. Mohl, Kenneth Matthews, and Vroni Hetherly*

1451 ECT and Parkinson's Disease Revisited: A "Naturalistic" Study *Richard Douyon, Michael Serby, Bruce Klutchko, and John Rotrosen*

1456 The Role of Social Relationships in the Course of First-Episode Schizophrenia and Affective Psychosis *David H. Erickson, Morton Beiser, William G. Iacono, Jonathan A.E. Fleming, and Tsung-yi Lin*

1462 Suicidality, Depression, and Substance Abuse in Adolescence *Janice C. Levy and Eva Y. Deykin*

1468 Psychiatric Disorders in the First-Degree Relatives of Probands With Bulimia Nervosa *Joy A. Kassett, Elliot S. Gershon, M. Elizabeth Maxwell, Juliet J. Guroff, Diane M. Kazuba, Anne L. Smith, Harry A. Brandt, and David C. Jimerson*

1472 Dementia With Coexistent Major Depression *Blaine S. Greenwald, Elisse Kramer-Ginsberg, Deborah B. Marin, Leila B. Laitman, Carol K. Hermann, Richard C. Mohs, and Kenneth L. Davis*

1479 Response to Sodium Lactate Infusion in Alcoholics With Panic Attacks *Deborah S. Cowley, Carl F. Jensen, Donald Johannessen, Lorne Parker, Stephen R. Dager, and R. Dale Walker*

1484 Exploring the Multidimensional Aspects of Grief Reactions *Luis A. Vargas, Fred Loya, and Janet Hodde-Vargas*

1489 Family Planning Needs of Female Chronic Psychiatric Outpatients *John H. Coverdale and John A. Aruffo*

COMMENTARY

1492 The Challenge of Relational Diagnoses: Applying the Biopsychosocial Model in *DSM-IV* *Group for the Advancement of Psychiatry Committee on the Family*

CLINICAL AND RESEARCH REPORTS

1495 Adjunctive Imipramine Maintenance Treatment in Schizophrenic Patients With Remitted Postpsychotic Depression *Samuel G. Siris, Janis Cutler, Kim Owen, Susan Mason, Susan Gingerich, and Mary Paige Lang*

1498 Perceptions of Parental Bonding in Borderline Patients *Joel Paris and Hallie Frank*

1500 Defense Styles Associated With Specific Anxiety Disorders *Christopher Pollock and Gavin Andrews*

BOOK FORUM 1503

LETTERS TO THE EDITOR 1515

1523 Corrections: Owen S. Surman: "Psychiatric Aspects of Organ Transplantation" (1989; 146:972–982); Lyman C. Wynne: review of *Marital and Family Therapy, 3rd ed.*, by Ira D. Glick, et al. (1989; 146:1223)

OFFICIAL ACTIONS

1524 Corporal Punishment in Schools
1525 The American Board of Psychiatry and Neurology, Inc.: Report on the April 1989 Examination

OTHER

A10 Officers of the American Psychiatric Association
A12 Calendar
A28 *British Journal of Psychiatry* Contents (September 1989)
A45 Information for Contributors
A50 Index to Advertisers

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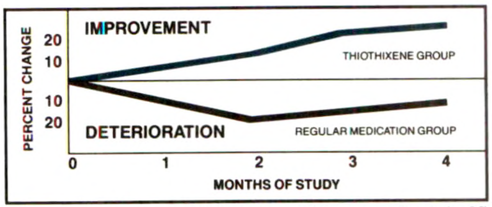

(Adapted from DiMascio and Demirgian[2,3])

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Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythimas).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

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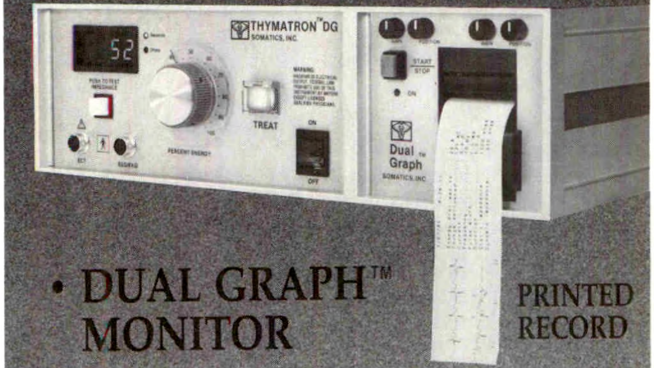

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Biological Priority and Psychological Supremacy: A New Integrative Paradigm Derived From Process Theory

By Hector C. Sabelli and Linnea Carlson-Sabelli

A Critical Review of Object Relations Theory

By N. Gregory Hamilton

Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, *1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to* Journal *readers will be included.*

JANUARY

January 20, annual meeting of the American Academy of Psychiatry and the Law, Tri-State Chapter, New York. Contact Howard Owens, M.D., The Forensic Psychiatry Clinic, 100 Centre Street, New York, NY 10013; 212-374-6260.

January 21–27, 16th Annual Meeting of the Southern Clinical Neurological Society, Islamorado, Florida. Contact Millie F. Walden, Executive Secretary, 3425 S.W. 2nd Avenue, #153, Gainesville, FL 32607; 904-374-6058 or 904-373-9765.

FEBRUARY

February 5–9, 12th Annual British Virgin Islands Medical Conference, Road Town, Tortola. Contact Butterworth Hospital, 100 Michigan, Northeast, Grand Rapids, Michigan; 616-732-2666.

February 12–14, 3rd Annual Research Conference on "A System of Care for Children: Building the Research Base," Tampa, Florida. Contact Alissa Algarin, RTCCMH, Florida Mental Health Institute, 13301 Bruce B. Downs Blvd., Tampa, FL 33612-3899; 813-974-4500.

February 16–18, 1st International Conference on Chronic Fatigue Syndrome and Fibromyalgia: Pathogenesis and Treatment, Los Angeles. Contact Richard Godwin, Chronic Fatigue Syndrome Institute, 436 North Roxbury, Suite 110, Beverly Hills, CA 90210; 213-394-3322.

MARCH

March 1–3, "Non-Epileptic (Pseudoepileptic) Seizures," sponsored by the American Epilepsy Society and the Epilepsy Foundation of America, Fort Lauderdale, Florida. Contact Mrs. Linda Tuchman, Neurology Service (127), VAMC, 130 West Kingsbridge Road, The Bronx, NY 10468; 212-584-9000 ext. 1885.

March 28–April 1, 18th Annual Meeting of the American Society for Psychosomatic Obstetrics and Gynecology, New York. Contact Patricia D. Stahr, Administrator, Liaison Activities, The American College of Obstetricians and Gynecologists, 409 12th Street, SW, Washington, DC 20024-2188; 202-863-2514.

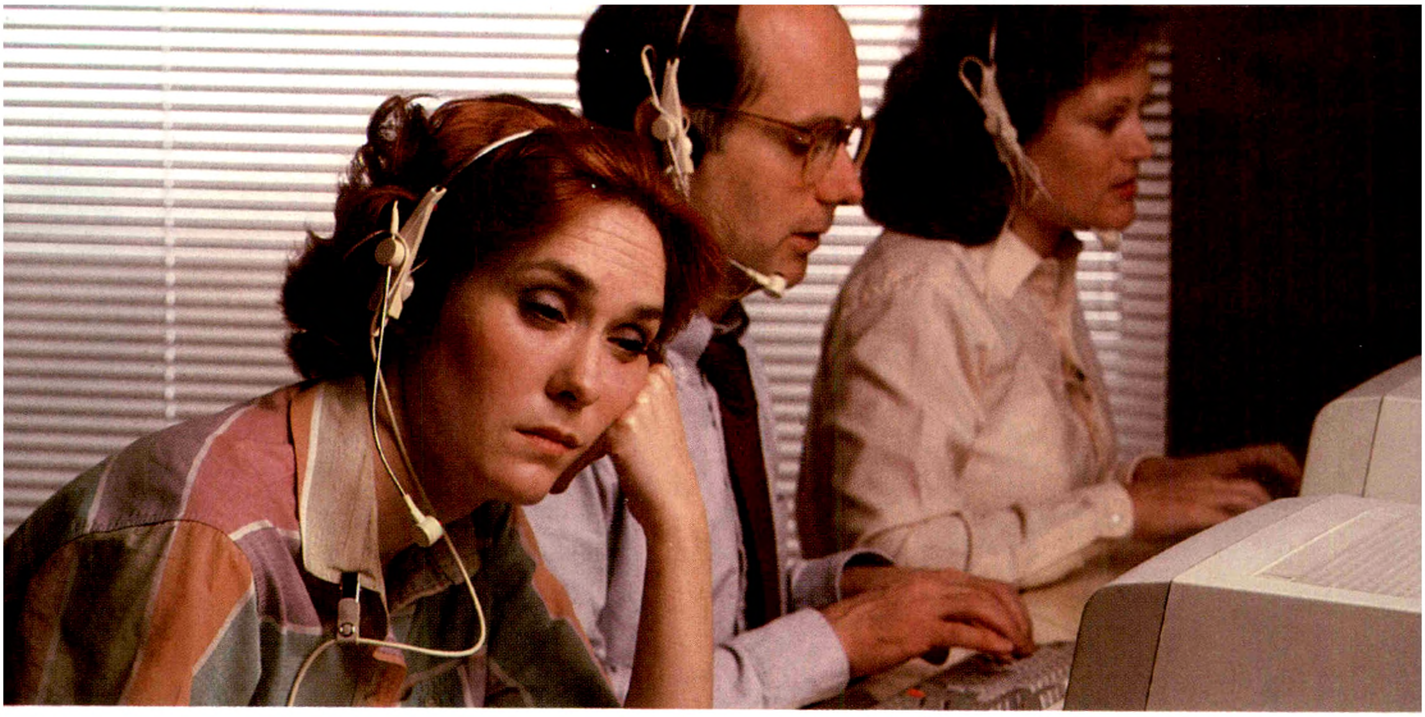
APRIL

April 4–6, International Symposium on New Concepts in Anxiety, Castres, France. Contact Martine Dehaye, Centre de Recherche Pierre Fabre, 17 avenue Jean Moulin, 81100 Castres, France; 63-35-56-07.

April 11–14, Asian Medicine: Past, Present and Future (Mental Health Care and Methods, Use of Medicinal Plants, Concepts and Applications of Acupuncture, and Other Alternative General Medical Practices), Bangkok, Thailand. Contact Ann McCormick, Southern California Neuropsychiatric Institute, 6794 La Jolla Blvd, La Jolla, CA 92037; 619-454-2102.

April 22–May 5, 2nd International Colloquium on Advances in Intensive Psychotherapy, Jerusalem. Contact David Fogel, M.D., 200 Fisher Building, Detroit, MI 48202.

April 25–27, 1st International Congress of Movement Disorders, Washington, D.C. Contact Mark Hallett, M.D., Scientific Secretariat, National Institute of Neurologic Disorders and Stroke, National Institutes of Health, Building 10, Room 5N226, Bethesda, MD 20892; or Secretariat ISMD, P.O. Box CH-4005, Basel, Switzerland.



Asleep at the switch.
This calls for a switch in antidepressants.

With PAMELOR there is little daytime sedation.[1-6]
Yet all the efficacy of amitriptyline.[7]

PAMELOR®
(nortriptyline HCl)

The active metabolite of amitriptyline

PAMELOR may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating heavy machinery or driving a car; therefore, the patient should be warned accordingly.

References: 1. Thompson TL II, Thompson WL. Treating depression: tricyclics, tetracyclics, and other options. *Modern Medicine.* August 1983;51:87-109. **2.** Georgotas A. Affective disorders: pharmacotherapy, In: Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry IV.* Baltimore, Md: Williams & Wilkins; 1985;1:821-833. **3.** Bye C, Clubley M, Peck AW. Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol.* 1978;6:155-161. **4.** Kupfer DJ, Spiker DG, Rossi A, Coble PA, Shaw D, Ulrich R. Nortriptyline and EEG sleep in depressed patients. *Biol Psychiatry.* 1982;17:535-546. **5.** Blackwell B, Peterson GR, Kuzma RJ, Hostetler RM, Adolph AB. The effect of five tricyclic antidepressants on salivary flow and mood in healthy volunteers. *Communications in Psychopharmacol.* 1980;4:255-261. **6.** Hayes PE, Kristoff CA. Adverse reactions to five new antidepressants. *Clin Pharm.* 1986;5:471-480. **7.** Ziegler VE, Clayton PJ, Biggs JT. A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry.* May 1977;34:607-612.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor® (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher A.U.C. and lower clearance of nortriptyline.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia. *Withdrawal Symptoms*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage.

[PAM-Z17—1/13/89]

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Corporation, E. Hanover, NJ 07936 (201) 503-7500

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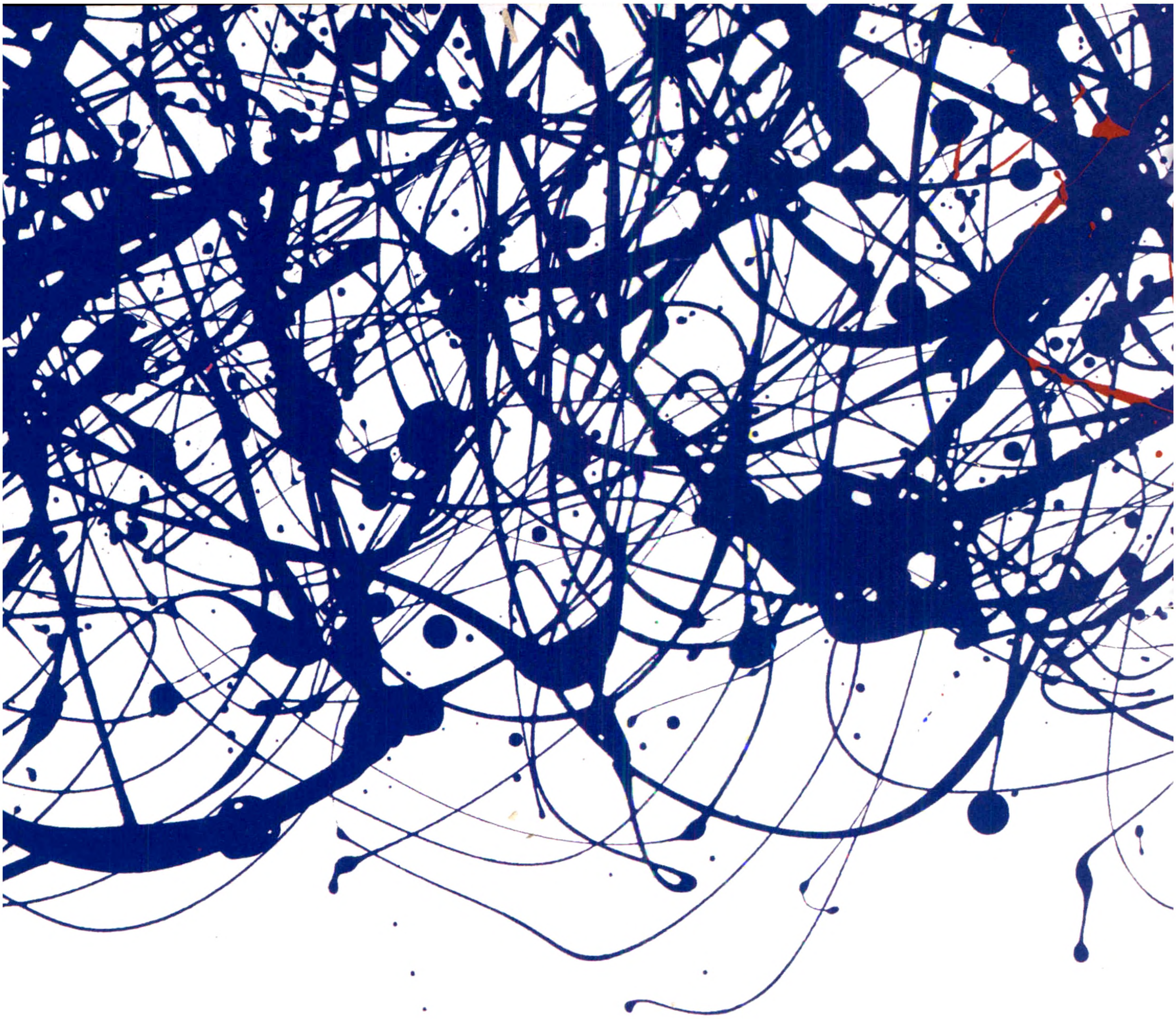


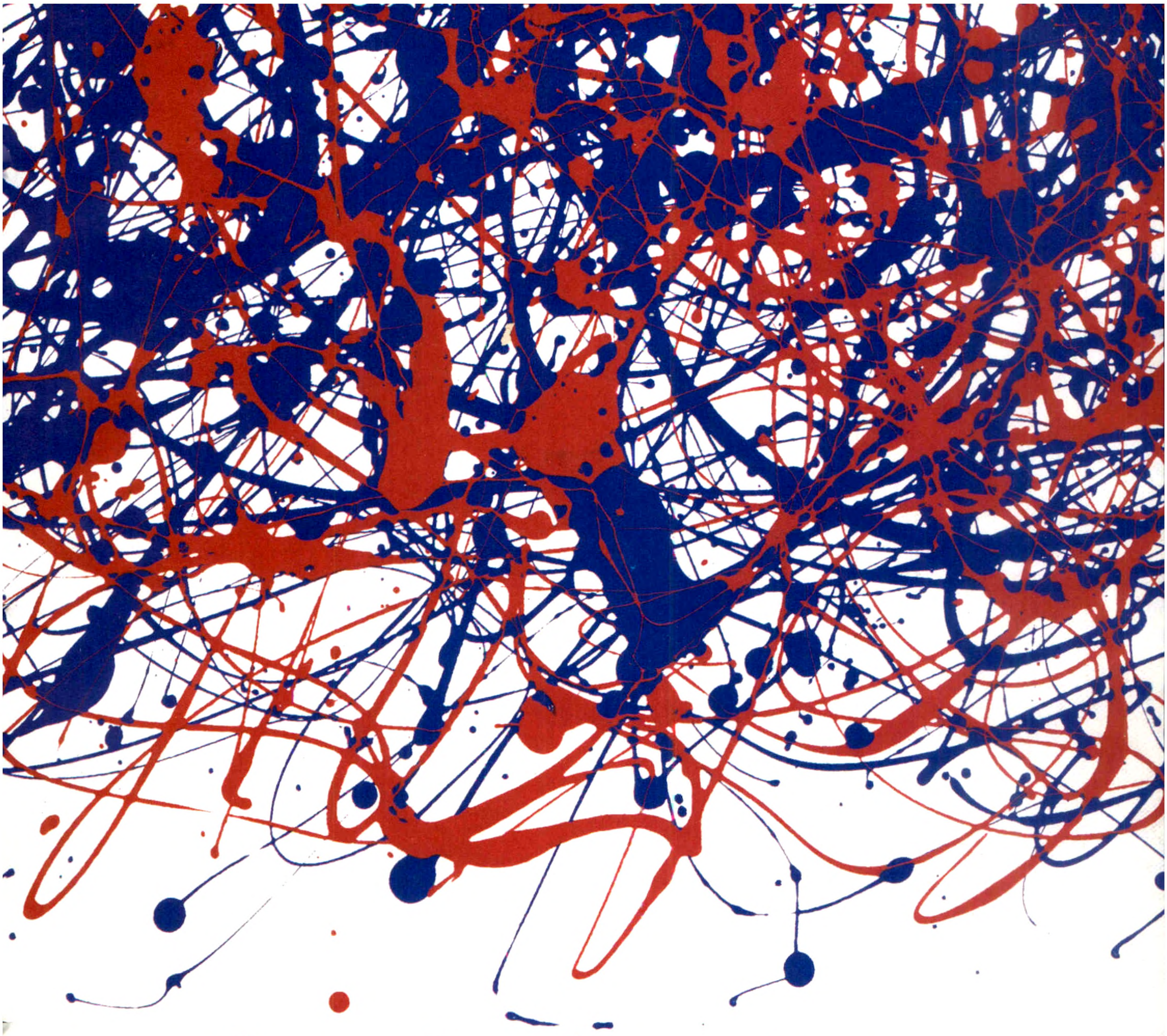
With depression . . .

In a clinical trial, XANAX was effective in reducing anxiety symptoms associated with moderate to severe depression.*

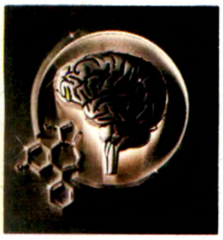
Patients taking XANAX should be alerted to possible additive CNS depressant effects when it is administered with other medications that produce CNS depression.

The usual starting dosage of XANAX is 0.25 to 0.5 mg t.i.d.

*Data on file, The Upjohn Company



you often find anxiety



TABLETS 0.5 MG

Xanax®

alprazolam Ⓘⓥ

For anxiety associated with depression

Upjohn Please see adjacent page for brief summary of prescribing information.

The Upjohn Company
Kalamazoo, Michigan 49001, USA

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XANAX® Tablets
(alprazolam, ©)

INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
XANAX is not of value in treating psychosis and should not be used in lieu of appropriate treatment. Patients receiving XANAX should be cautioned about hazardous occupations or activities requiring full alertness and also about simultaneous ingestion of alcohol or other CNS depressants.

Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions.) Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings.) Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-8-S
J-2252
November, 1989

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Could you use the APA's assistance in planning, improving services or solving a problem at your hospital or facility?

This long-standing program of the APA provides **confidential** consultations to all mental health care organizations on topics ranging from low utilization of beds to disagreement among staff about methods of treatment.

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OW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENTS

Feeling better
Living better

NEW **Wellbutrin**®

(BUPROPION HCl)

helps clear depression with few life-style disruptions.

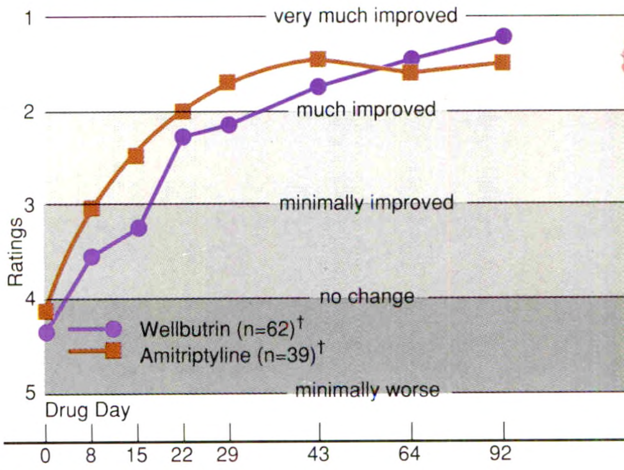
See brief summary of full prescribing information on last pages of this advertisement.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENT

Chemically unique WELLBUTRIN is unrelated to tricyclics/tetracyclics, monoamine oxidase inhibitors, or other known antidepressants.

WELLBUTRIN relieves depression as effectively as amitriptyline.

Clinical Global Improvement*



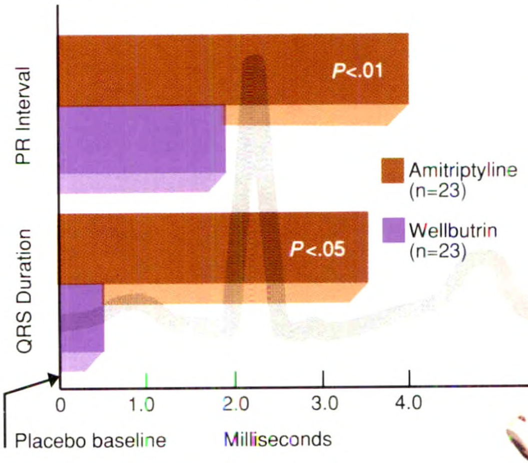
* Adapted from Mendels et al.[1]

†Dosages were 300 to 450 mg/day for WELLBUTRIN, 75 to 150 mg/day for amitriptyline.

Please review IMPORTANT CONSIDERATIONS BEFORE PRESCRIBING WELLBUTRIN on page 6 and brief summary on the last pages of this advertisement before prescribing WELLBUTRIN.

WELLBUTRIN relieves depression with no clinically significant effect on cardiac conduction.

Average Change in EKG Parameters from Baseline Values During Treatment*



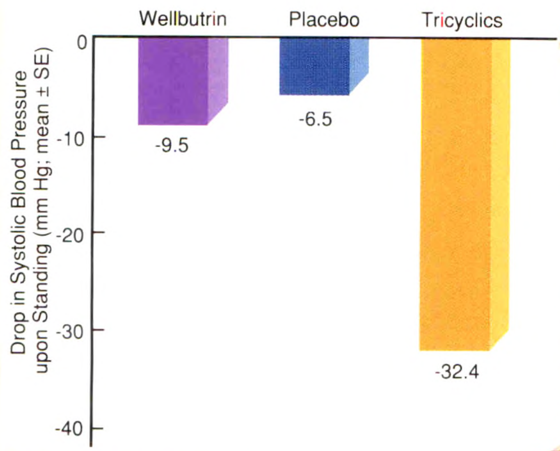
* Adapted from Wenger et al.[2]

"By contrast, the present results with bupropion support the in vitro data demonstrating that this antidepressant lacks these undesirable electro-physiologic properties, and imply that bupropion has a substantially wider margin of safety in man than amitriptyline with regard to cardiac conduction."[2]

Feeling better
Living better

WELLBUTRIN relieves depression with no clinically significant orthostatic hypotension.

Orthostatic Blood Pressure Change (mm Hg)*



* Adapted from Farid et al.[3]

NEW Wellbutrin®

(BUPROPION HCl)

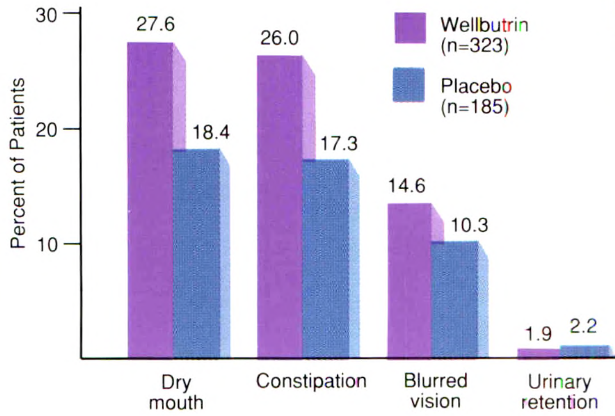
Helps clear depression with few life-style disruptions.

See brief summary of full prescribing information on last pages of this advertisement.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENT

WELLBUTRIN relieves depression with few anticholinergic side effects.

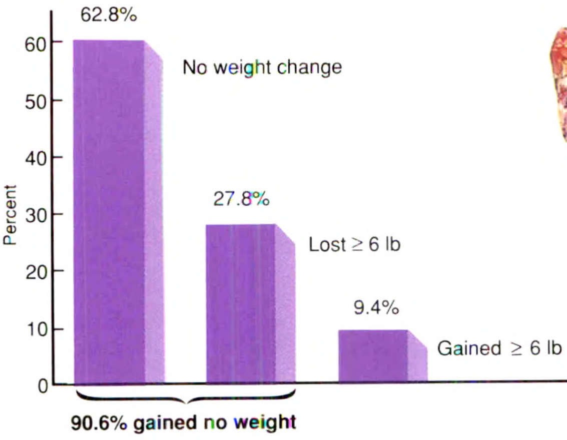
Percent Difference in Anticholinergic Effects Relative to Placebo*



* Data on file, Burroughs Wellcome Co.[4]

WELLBUTRIN relieves depression with little or no weight gain.

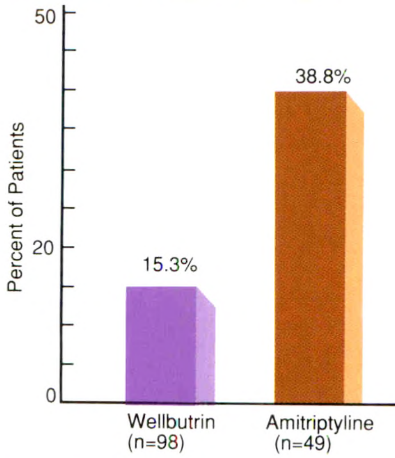
Change in Body Weight (percent of patients; n=341)*



* Data on file, Burroughs Wellcome Co.[4]

Feeling better
Living better

WELLBUTRIN relieves depression with little or no daytime drowsiness.


Percent of Patients Reporting Treatment-Related Drowsiness*

* Data on file, Burroughs Wellcome Co.[4]

In placebo-controlled clinical trials, the incidence of drowsiness* for patients treated with WELLBUTRIN was 19.8%, versus 19.5% for those receiving placebo.

Agitation and Insomnia: A substantial proportion of patients treated with WELLBUTRIN experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of WELLBUTRIN treatment.

**As with all drugs in this category, patients should be cautioned that the ability to perform tasks requiring judgment or motor and cognitive skills may be impaired.*

NEW Wellbutrin®
(BUPROPION HCl)

Helps clear depression with few life-style disruptions.

See brief summary of full prescribing information on last pages of this advertisement.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENT

Feeling better
Living better

Wellbutrin® helps clear depression with few life-style disruptions.

Important considerations before prescribing Wellbutrin.

Patient Selection Criteria
WELLBUTRIN is contraindicated in patients

- with a seizure disorder
- with a current or prior diagnosis of bulimia or anorexia nervosa
- on monoamine oxidase (MAO) inhibitor therapy
- who are allergic to it

(See CONTRAINDICATIONS section of full prescribing information.)

WELLBUTRIN should be administered with extreme caution to patients

- with a history of seizure, cranial trauma, or other factors that predispose toward seizure
- taking other agents or other treatment regimens that may lower seizure threshold

(See WARNINGS section of full prescribing information.)

Overdosage
In 13 cases of overdose involving WELLBUTRIN, there were no deaths or lasting sequelae.

Seizures
A wide range of seizure rates have been reported with antidepressant therapy with some reports as low as 0.1%. The incidence of seizures with WELLBUTRIN is approximately 0.4%, which may be as much as fourfold higher than some other antidepressants, although no direct comparative studies have been conducted.

Dosage and Administration
The recommended starting dose of WELLBUTRIN is 200 mg/day given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day given as 100 mg t.i.d. no sooner than three days after beginning therapy.

Dosing Regimen

Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets Morning	Midday	Evening
1-3	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Increases in dose should not exceed 100 mg/day in a three-day period. WELLBUTRI is available in both 75 mg and 100 mg tablets.

Important: No single dose of WELLBUTRIN should exceed 150 mg because a higher incidence of seizures has been observed in patients receiving higher individual doses of WELLBUTRIN. For this reason, too, patients should be reminded that they should not double up on any dose because they missed a previous one. Dosage should not exceed 450 mg per day (see WARNINGS).

Clinical trials involving more than 7,000 depressed patients and over 200 investigators demonstrated that **WELLBUTRIN relieves depression in a wide range of patients:**

- with no clinically significant effects on cardiac conduction
- with no clinically significant orthostatic hypotension
- with few anticholinergic side effects
- with little or no weight gain
- with little or no daytime drowsiness

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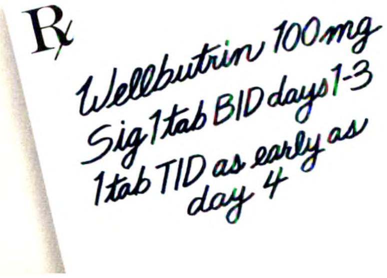

℞
Wellbutrin 100mg
Sig 1 tab BID days 1-3
1 tab TID as early as
day 4

See brief summary of full prescribing informat on last pages of this advertisement.

WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Wellbutrin is indicated for the treatment of depression. A physician considering the initiation of Wellbutrin should be aware that the drug may cause generalized seizures with an approximate incidence of 0.4% (4/1000). This incidence may exceed that of other antidepressants as much as fourfold. This relative risk is only an approximation since no direct comparative studies have been conducted.

CONTRAINDICATIONS: Wellbutrin is contraindicated in patients: with a seizure disorder; with a current or prior diagnosis of bulimia or anorexia nervosa, because of a higher incidence of seizures noted in such patients; who have shown an allergic response to it; or who are currently being treated with an MAO inhibitor. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Wellbutrin.

WARNINGS:

SEIZURES: Wellbutrin is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for Wellbutrin increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third the maximum recommended daily dose (450 mg). Given the wide variability among individuals and their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

During the pre-approval evaluation period, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, 7 patients were receiving daily doses of 450 mg or below, for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve (12) patients experienced seizures at 600 mg per day (2.3% incidence); 6 additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

A separate, prospective study was conducted to determine the incidence of seizure during an 8 week treatment exposure in approximately 3200 additional patients who received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond 8 weeks if clinically indicated. Eight (8) seizures occurred during the initial 8 week treatment period and 5 seizures were reported in patients continuing treatment beyond 8 weeks, resulting in a total seizure incidence of 0.4%.

The risk of seizure appears to be strongly associated with dose and the presence of predisposing factors. A significant predisposing factor (e.g., history of head trauma or prior seizure, CNS tumor, concomitant medications that lower seizure threshold, etc.) was present in approximately one-half of the patients experiencing a seizure. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose.

Recommendations for reducing the risk of seizure: **Retrospective analysis of clinical experience gained during the development of Wellbutrin suggests that the risk of seizure may be minimized if (1) the total daily dose of Wellbutrin does *not* exceed 450 mg, (2) the daily dose is administered t.i.d., with each single dose *not* to exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites, and (3) the rate of incrementation of dose is very gradual. Extreme caution should be used when Wellbutrin is (1) administered to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or (2) prescribed with other agents (e.g., antipsychotics, other antidepressants, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.**

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatotoxin in humans.

PRECAUTIONS:

General:

Agitation and Insomnia: A substantial proportion of patients treated with Wellbutrin experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of Wellbutrin treatment.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Patients treated with Wellbutrin have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Wellbutrin. In several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in Bipolar Manic Depressive patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin is expected to pose similar risks.

Altered Appetite and Weight: A weight loss of greater than 5 pounds occurred in 28% of Wellbutrin patients. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 34.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with Wellbutrin did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of Wellbutrin should be considered.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for Wellbutrin should be written for the smallest number of tablets consistent with good patient management.

Use in Patients with Systemic Illness: There is no clinical experience establishing the safety of Wellbutrin in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Wellbutrin was well tolerated in patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants.

Because bupropion HCl and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients beyond concentrations expected in patients without renal or hepatic impairment. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

Information for Patients:

Patients should be instructed to take Wellbutrin in equally divided doses three or four times a day to minimize the risk of seizure.

Patients should be told that any CNS-active drug like Wellbutrin may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that Wellbutrin does not adversely affect their performance they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the use and cessation of use of alcohol may alter the seizure threshold, and, therefore, that the consumption of alcohol should be minimized, and, if possible, avoided completely.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Drug Interactions: No systematic data have been collected on the consequences of the concomitant administration of Wellbutrin and other drugs.

However, animal data suggest that Wellbutrin may be an inducer of drug metabolizing enzymes. This may be of potential clinical importance because the blood levels of co-administered drugs may be altered.

Alternatively, because bupropion is extensively metabolized, the co-administration of other drugs may affect its clinical activity. In particular, care should be exercised when administering drugs known to affect hepatic drug metabolizing enzyme systems (e.g., carbamazepine, cimetidine, phenobarbital, phenytoin).

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of Wellbutrin and L-dopa. Administration of Wellbutrin to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small gradual dose increases.

Concurrent administration of Wellbutrin and agents which lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and small gradual dose increases should be employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a borderline positive response (2-3 times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance of these results in estimating the risk of human exposure to therapeutic doses is unknown.

A fertility study was performed in rats; no evidence of impairment of fertility was encountered at oral doses up to 300 mg/kg/day.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B: Reproduction studies have been performed in rabbits and rats at doses up to 15-45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in two studies, but there was no increase in any specific abnormality). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: The effect of Wellbutrin on labor and delivery in humans is unknown.

Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from Wellbutrin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of Wellbutrin in individuals under 18 years old have not been established.

Use in the Elderly: Wellbutrin has not been systematically evaluated in older patients.

ADVERSE REACTIONS: (See also WARNINGS and PRECAUTIONS) Adverse events commonly encountered in patients treated with Wellbutrin are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

Adverse events were sufficiently troublesome to cause discontinuation of Wellbutrin treatment in approximately ten percent of the 2400 patients and volunteers who participated in the product's pre-approval clinical trials. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENT

The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Wellbutrin under relatively similar conditions of daily dosage (300-600 mg), setting, and duration (3-4 weeks). The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of Wellbutrin is provided in the WARNINGS and PRECAUTIONS sections.

TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS*
(Percent of Patients Reporting)

Adverse Experience	**Wellbutrin Patients (n = 323)**	**Placebo Patients (n = 185)**
CARDIOVASCULAR		
Cardiac Arrhythmias	5.3	4.3
Dizziness	22.3	16.2
Hypertension	4.3	1.6
Hypotension	2.5	2.2
Palpitations	3.7	2.2
Syncope	1.2	0.5
Tachycardia	10.8	8.6
DERMATOLOGIC		
Pruritus	2.2	0.0
Rash	8.0	6.5
GASTROINTESTINAL		
Anorexia	18.3	18.4
Appetite Increase	3.7	2.2
Constipation	26.0	17.3
Diarrhea	6.8	8.6
Dyspepsia	3.1	2.2
Nausea/Vomiting	22.9	18.9
Weight Gain	13.6	22.7
Weight Loss	23.2	23.2
GENITOURINARY		
Impotence	3.4	3.1
Menstrual Complaints	4.7	1.1
Urinary Frequency	2.5	2.2
Urinary Retention	1.9	2.2
MUSCULOSKELETAL		
Arthritis	3.1	2.7
NEUROLOGICAL		
Akathisia	1.5	1.1
Akinesia/Bradykinesia	8.0	8.6
Cutaneous Temperature Disturbance	1.9	1.6
Dry Mouth	27.6	18.4
Excessive Sweating	22.3	14.6
Headache/Migraine	25.7	22.2
Impaired Sleep Quality	4.0	1.6
Increased Salivary Flow	3.4	3.8
Insomnia	18.6	15.7
Muscle Spasms	1.9	3.2
Pseudoparkinsonism	1.5	1.6
Sedation	19.8	19.5
Sensory Disturbance	4.0	3.2
Tremor	21.1	7.6
NEUROPSYCHIATRIC		
Agitation	31.9	22.2
Anxiety	3.1	1.1
Confusion	8.4	4.9
Decreased Libido	3.1	1.6
Delusions	1.2	1.1
Disturbed Concentration	3.1	3.8
Euphoria	1.2	0.5
Hostility	5.6	3.8
NONSPECIFIC		
Fatigue	5.0	8.6
Fever/Chills	1.2	0.5
RESPIRATORY		
Upper Respiratory Complaints	5.0	11.4
SPECIAL SENSES		
Auditory Disturbance	5.3	3.2
Blurred Vision	14.6	10.3
Gustatory Disturbance	3.1	1.1

*Events reported by at least 1% of Wellbutrin patients are included.

Other events observed during the entire pre-approval evaluation of Wellbutrin: During its pre-approval assessment, Wellbutrin was evaluated in almost 2400 subjects. The conditions and duration of exposure to Wellbutrin varied greatly and a substantial proportion of the experience was gained in open and uncontrolled clinical settings. During this experience, numerous adverse events were reported; however, without appropriate controls, it is impossible to determine with certainty which events were or were not caused by Wellbutrin. The following enumeration is organized by organ system and describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections of the labeling.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular: Frequent was edema; infrequent were chest pain, EKG abnormalities (premature beats and nonspecific ST-T changes), and shortness of breath/dyspnea; and rare were pallor and phlebitis.

Dermatologic: Frequent were nonspecific rashes; infrequent were alopecia and dry skin; rare were change in hair color and hirsutism.

Endocrine: Infrequent was gynecomastia; rare were glycosuria and hormone level change.

Gastrointestinal: Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice; rare were rectal complaints, colitis, G.I. bleeding, and intestinal perforation.

Genitourinary: Frequent was nocturia; infrequent were vaginal irritation, testicular swelling, urinary tract infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia, and painful ejaculation.

Hematologic/Oncologic: Rare was lymphadenopathy.

Neurological: (see WARNINGS) Frequent were ataxia/incoordination, seizure, myoclonus, dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; and rare were EEG abnormality, abnormal neurological exam, impaired attention, and sciatica.

Neuropsychiatric: (see PRECAUTIONS) Frequent were mania/hypomania, increased libido, hallucinations, decrease in sexual function, and depression; infrequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder, and frigidity; rare was suicidal ideation.

Oral Complaints: Frequent was stomatitis; infrequent were toothache, bruxism, gum irritation, and oral edema; rare was glossitis.

Respiratory: Infrequent were bronchitis and shortness of breath/dyspnea; rare were epistaxis and rate or rhythm disorder.

Special Senses: Infrequent was visual disturbance; rare was diplopia.

Nonspecific: Frequent were flu-like symptoms; infrequent was nonspecific pain; rare wer body odor, surgically related pain, infection, medication reaction and overdose.

Post-Approval Reports: The following additional events were rarely observed (less tha 1/1000 patients) post-approval.

Cardiovascular: Flushing and myocardial infarction.

Dermatologic: Acne.

Gastrointestinal: Stomach ulcer.

Hematologic/Oncologic: Anemia and pancytopenia.

Neurological: Aphasia.

Musculoskeletal: Musculoskeletal chest pain.

Respiratory: Pneumonia and pulmonary embolism.

OVERDOSAGE:

Human overdose experience: There has been limited clinical experience with overdosag of Wellbutrin. Thirteen overdoses occurred during clinical trials. Twelve patients ingeste 850 to 4200 mg and recovered without significant sequelae. Another patient who ingeste 9000 mg of Wellbutrin and 300 mg of tranylcypromine experienced a grand mal seizur and recovered without further sequelae.

DOSAGE AND ADMINISTRATION:

General Dosing Considerations: It is particularly important to administer Wellbutrin in a mar ner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose shoul not exceed 100 mg/day in a 3 day period. Gradual escalation in dosage is also importa if agitation, motor restlessness, and insomnia, often seen during the initial days of treat ment, are to be minimized. If necessary, these effects may be managed by temporary reduc tion of dose or the short-term administration of an intermediate to long-acting sedative hyp notic. A sedative hypnotic usually is not required beyond the first week of treatment. I somnia may also be minimized by avoiding bedtime doses. If distressing, untoward effect supervene, dose escalation should be stopped.

No single dose of Wellbutrin should exceed 150 mg. Wellbutrin should be administered t.i.d. preferably with at least 6 hours between successive doses.

Usual Dosage for Adults: The usual adult dose is 300 mg/day, given t.i.d. Dosing shoul begin at 200 mg/day, given as 100 mg b.i.d. Based on clinical response, this dose ma be increased to 300 mg/day, given as 100 mg t.i.d., no sooner than 3 days after beginnin therapy (see table below).

Dosing Regimen

Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets		
			Morning	Midday	Evenin
1	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

Increasing the Dosage Above 300 mg/Day: As with other antidepressants, the full a tidepressant effect of Wellbutrin may not be evident until 4 weeks of treatment or longe An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not mo than 150 mg each, may be considered for patients in whom no clinical improvement is note after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be a complished using the 75 or 100 mg tablets. The 100 mg tablet must be administered q.i. with at least 4 hours between successive doses, in order not to exceed the limit of 150 in a single dose. Wellbutrin should be discontinued in patients who do not demonstrate adequate response after an appropriate period of treatment at 450 mg/day.

Elderly Patients: In general, older patients are known to metabolize drugs more slowly a to be more sensitive to the anticholinergic, sedative, and cardiovascular side effects of a tidepressant drugs.

References: **1.** Mendels J, Amin MM, Chouinard G, et al. A comparative study of bupropion and amitriptyline in depressed outpatients. *J Clin Psychiatry.* 1983;44(5, sec 2):118-120. **2.** Wen TL, Cohn JB, Bustrack J. Comparison of the effects of bupropion and amitriptyline on cardiac conduction in depressed patients. *J Clin Psychiatry.* 1983;44(5, sec 2):174-175. **3.** Farid FF, Wenger Tsai SY, et al. Use of bupropion in patients who exhibit orthostati hypotension on tricyclic antidepressants. *J Clin Psychiatry.* 1983; (5, sec 2):170-173. **4.** Data on file, Burroughs Wellcome Co.

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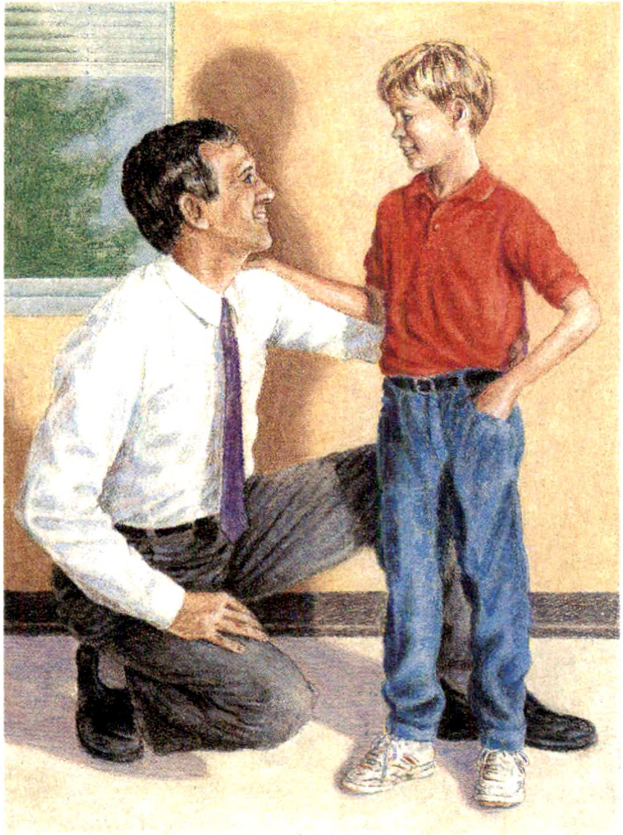

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Annotation

Foetal learning: implications for psychiatry? *P.G. Hepper* 289

Review Articles

The genetics of depression and manic-depressive disorder. *P. McGuffin and R. Katz* 294

Beyond the dopamine hypothesis. The neurochemical pathology of schizophrenia. *G.P. Reynolds* 305

Papers

The Guy's/Age Concern survey. Prevalence rates of cognitive impairment, depression and anxiety in an urban elderly community. *J. Lindesay, K. Briggs and E. Murphy* 317

Depression before and after age 65. A re-examination. *L. Musetti, G. Perugi, A. Soriani, V.M. Rossi, G.B. Cassano and H.S. Akiskal* 330

Socio-cultural parameters in Yoruba Nigerian patients with affective disorders. *R.O.A. Makanjuola* 337

A study of the effects of desipramine treatment alone and in combination with L-triiodothyronine on 6-sulphatoxymelatonin excretion in depressed patients. *J. Bearn, C. Franey, J. Arendt and S.A. Checkley* 341

The Scottish survey of new chronic in-patients: five-year follow-up. *R.G. McCreadie and E. McCannell* 348

The significance of stupor in the long-term outcome of chronic schizophrenia. *J.C. Rigby, S.M. Wood and R.H.S. Mindham* 352

Maternity blues.
- I. Detection and measurement by questionnaire. *H. Kennerley and D. Gath* 356
- II. A comparison between post-operative women and post-natal women. *S. Iles, D. Gath and H. Kennerley* 363
- III. Associations with obstetric, psychological, and psychiatric factors. *H. Kennerley and D. Gath* 367

Sexual anxiety in sexual dysfunction. *D.G. Patterson and E.C. O'Gorman* 374

Measuring behaviour disorder in mental handicap. *J. Lund* 379

Violence by psychiatric in-patients. *P. Noble and S. Rodger* 384

Point of View

Hysteria, belief, and magic. *D.C. Taylor* 391

Brief Reports

Paedophilia: cognitive/behavioural treatment approach in a single case. *S.J. Enright* 399

Musical hallucinations in a deaf elderly woman. *G.W. Fenton and D.A. McRae* 401

Social phobia secondary to pathological sweating. *M.J. Edlund* 403

A family with Alzheimer's disease. *S.V. Patel* 405

Pericentric inversion chromosome 9 and personality disorder. *H.V. Kumar, K.J. McMahon, K.M. Allman, B. McCaffrey and A. Rowan* 408

Psychiatric features of adult GM_2 gangliosidosis. *J. Streifler, M. Golomb and N. Gadoth* 410

Adverse interaction between cimetidine and chlorpromazine in two cases of chronic schizophrenia. *A. Byrne and B. O'Shea* 413

Mianserin-induced restless legs syndrome. *I. Paik, C. Lee, B. Choi, Y. Chae and C. Kim* 415

Correspondence

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Book Reviews

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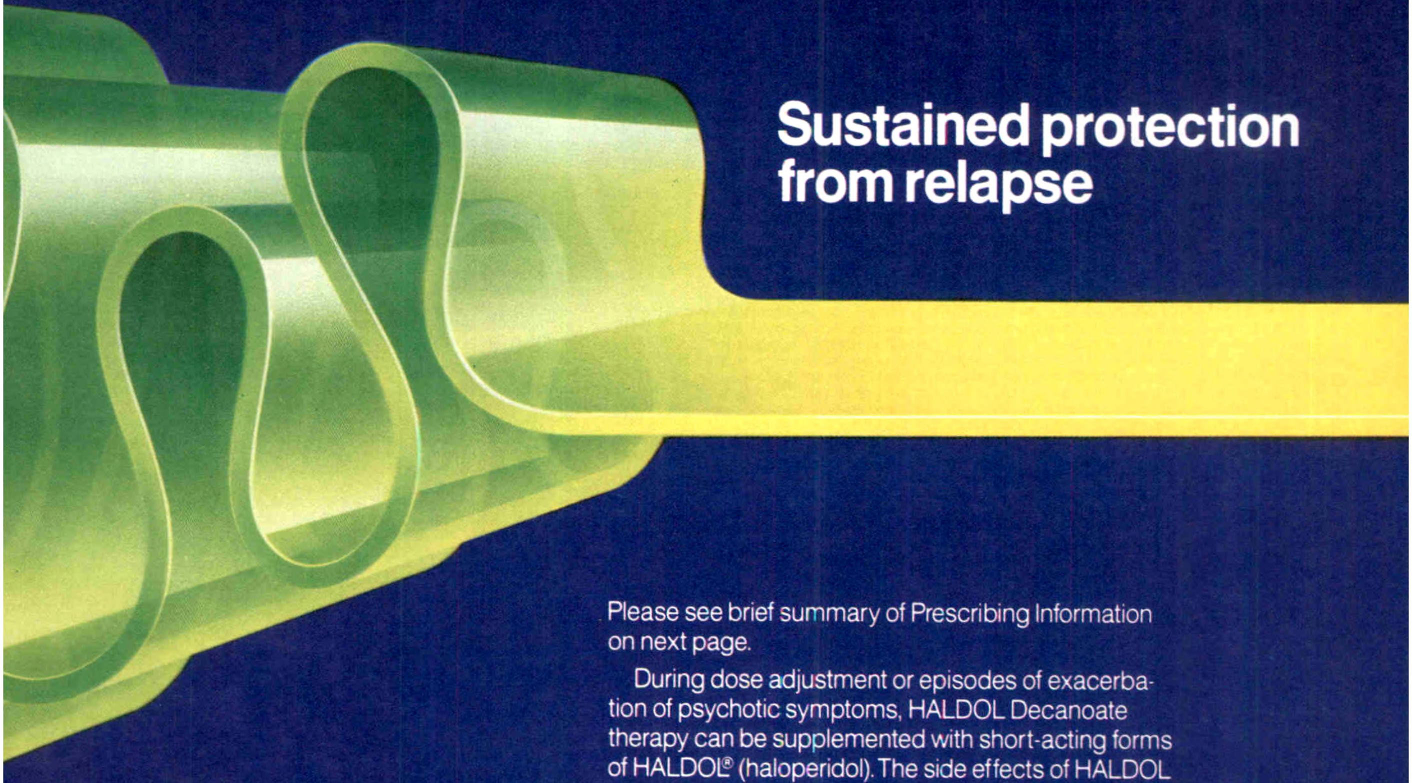

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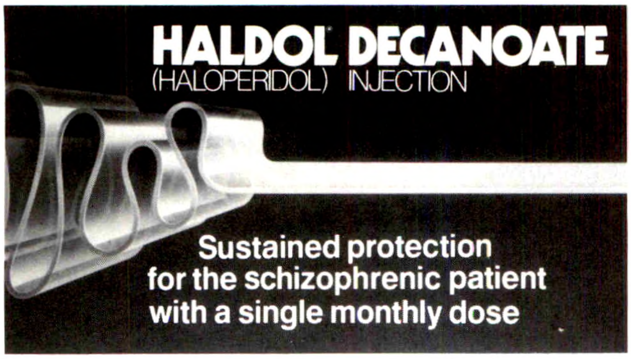

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia*—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

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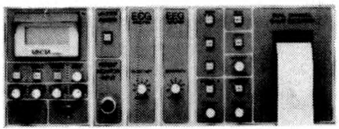

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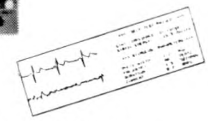

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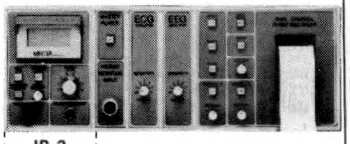

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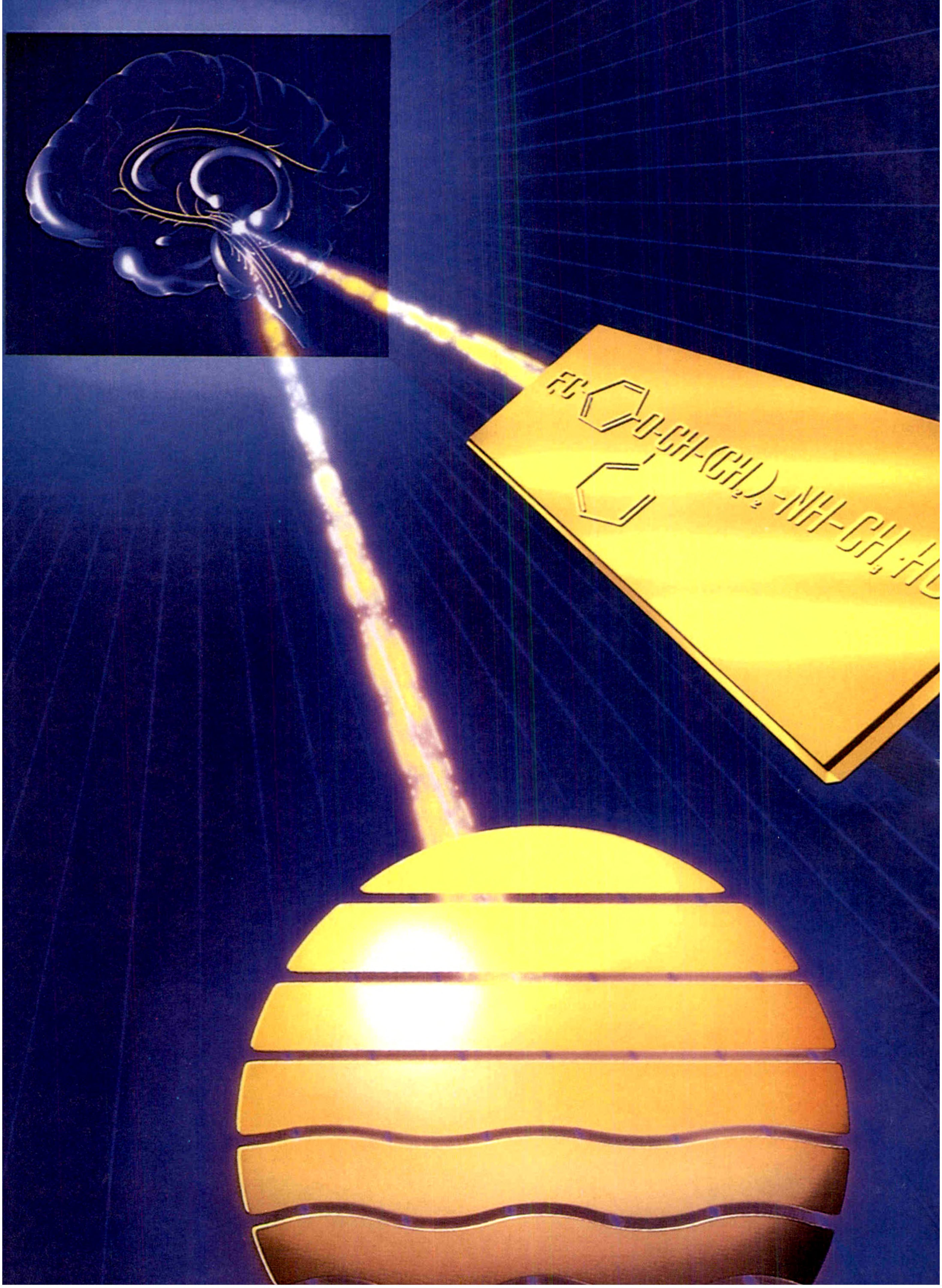
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[1] *Curr Ther Res* 1986;39:559–563.
*As defined by DSM-III.

See adjacent page for brief summary of prescribing information.

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Prozac®

fluoxetine hydrochloride

Brief Summary: Consult the package literature for complete prescribing information.

Indication: Prozac is indicated for the treatment of depression.

Contraindication: Prozac is contraindicated in patients known to be hypersensitive to it.

Warnings: *Monoamine Oxidase Inhibitors* — Data on the effects of the combined use of fluoxetine and MAO inhibitors are limited. Their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI. Administration of an MAOI within five weeks of discontinuation of fluoxetine may increase the risk of serious events. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine.

Rash and Accompanying Events — During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknowable at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: *General* — Anxiety and Insomnia — Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight — Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with Prozac compared to 4% of placebo- and 3% of tricyclic-antidepressant-treated patients. However, only rarely have patients been discontinued from treatment with Prozac because of weight loss.

Activation of Mania/Hypomania — During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures — Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide — The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites — Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (*see* Clinical Pharmacology *and* Dosage and Administration).

Use in Patients With Concomitant Illness — Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has **not** been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference With Cognitive and Motor Performance — Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients — Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests — There are no specific laboratory tests recommended.

Drug Interactions — As with all drugs, the potential for interaction by a variety of mechanisms (ie, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc) is a possibility (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Tryptophan — Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors — *See* Warnings.

Other Antidepressants — There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Diazepam Clearance — The half-life of concurrently administered diazepam may be prolonged in some patients (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins — Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

CNS-Active Drugs — The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Electroconvulsive Therapy — There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility — There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy — Teratogenic Effects — Pregnancy Category B — Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery — The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers — It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children — Safety and effectiveness in children have not been established.

Usage in the Elderly — Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Hyponatremia — Several cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

Adverse Reactions: *Commonly Observed* — The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment — Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

TABLE 1. TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event*	Percentage of Patients Reporting Event	
	Prozac (N = 1,730)	Placebo (N = 799)
Nervous		
Headache	20.3	15.5
Nervousness	14.9	8.5
Insomnia	13.8	7.1
Drowsiness	11.6	6.3
Anxiety	9.4	5.5
Tremor	7.9	2.4
Dizziness	5.7	3.3
Fatigue	4.2	1.1
Sedated	1.9	1.3
Sensation disturbance	1.7	2.0
Libido, decreased	1.6	—
Lightheadedness	1.6	—
Concentration, decreased	1.5	—
Digestive		
Nausea	21.1	10.1
Diarrhea	12.3	7.0
Mouth dryness	9.5	6.0
Anorexia	8.7	1.5
Dyspepsia	6.4	4.3
Constipation	4.5	3.3
Pain, abdominal	3.4	2.9
Vomiting	2.4	1.3
Taste change	1.8	—
Flatulence	1.6	1.1
Gastroenteritis	1.0	1.4
Skin and Appendages		
Sweating, excessive	8.4	3.8
Rash	2.7	1.8
Pruritus	2.4	1.4
Body as a Whole		
Asthenia	4.4	1.9
Infection, viral	3.4	3.1
Pain, limb	1.6	1.1
Fever	1.4	—
Pain, chest	1.3	1.1
Allergy	1.2	1.1
Influenza	1.2	1.5
Respiratory		
Upper respiratory infection	7.6	6.0
Flu-like syndrome	2.8	1.9
Pharyngitis	2.7	1.3
Nasal congestion	2.6	2.3
Headache, sinus	2.3	1.8
Sinusitis	2.1	2.0
Cough	1.6	1.6
Dyspnea	1.4	—
Cardiovascular		
Hot flushes	1.8	1.0
Palpitations	1.3	1.4
Musculoskeletal		
Pain, back	2.0	2.4
Pain, joint	1.2	1.1
Pain, muscle	1.2	1.0
Urogenital		
Menstruation, painful	1.9	1.4
Sexual dysfunction	1.9	—
Frequent micturition	1.6	—
Urinary tract infection	1.2	—
Special Senses		
Vision disturbance	2.8	1.8

*Events reported by at least 1% of Prozac-treated patients are included.
— Incidence less than 1%.

Incidence in Controlled Clinical Trials — Table 1 enumerates adverse events that occurred at a frequency of 1% or more among Prozac-treated patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Other Events Observed During the Premarketing Evaluation of Prozac — During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 individuals exposed to Prozac who experienced an event of the type cited on at least one occasion while receiving Prozac. All reported events are included except those already listed in tables, those COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole — *Frequent:* chills; *Infrequent:* chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; *Rare:* abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System — *Infrequent:* angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; *Rare:* AV block (first-degree), bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System — *Frequent:* increased appetite; *Infrequent:* aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, and thirst; *Rare:* bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

Endocrine System — *Infrequent:* hypothyroidism; *Rare:* goiter and hyperthyroidism.

Hemic and Lymphatic System — *Infrequent:* anemia and lymphadenopathy; *Rare:* bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocythemia.

Metabolic and Nutritional — *Frequent:* weight loss; *Infrequent:* generalized edema, hypoglycemia, peripheral edema, and weight gain; *Rare:* dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficiency anemia.

Musculoskeletal System — *Infrequent:* arthritis, bone pain, bursitis, tenosynovitis, and twitching; *Rare:* bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System — *Frequent:* abnormal dreams and agitation; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System — *Frequent:* bronchitis, rhinitis, and yawn; *Infrequent:* asthma, epistaxis, hiccup, hyperventilation, and pneumonia; *Rare:* apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, and pleural effusion.

Skin and Appendages — *Infrequent:* acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; *Rare:* eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses — *Infrequent:* amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; *Rare:* blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System — *Infrequent:* abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; *Rare:* abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postintroduction Reports — Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: vaginal bleeding after drug withdrawal, hyperprolactinemia, and thrombocytopenia.

Overdosage: *Human Experience* — As of December 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L respectively. A second death involved three drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.80 mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (*see* Management of Overdose). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without residua.

PV 2472 DPP [111788]

Additional information available to the profession on request from

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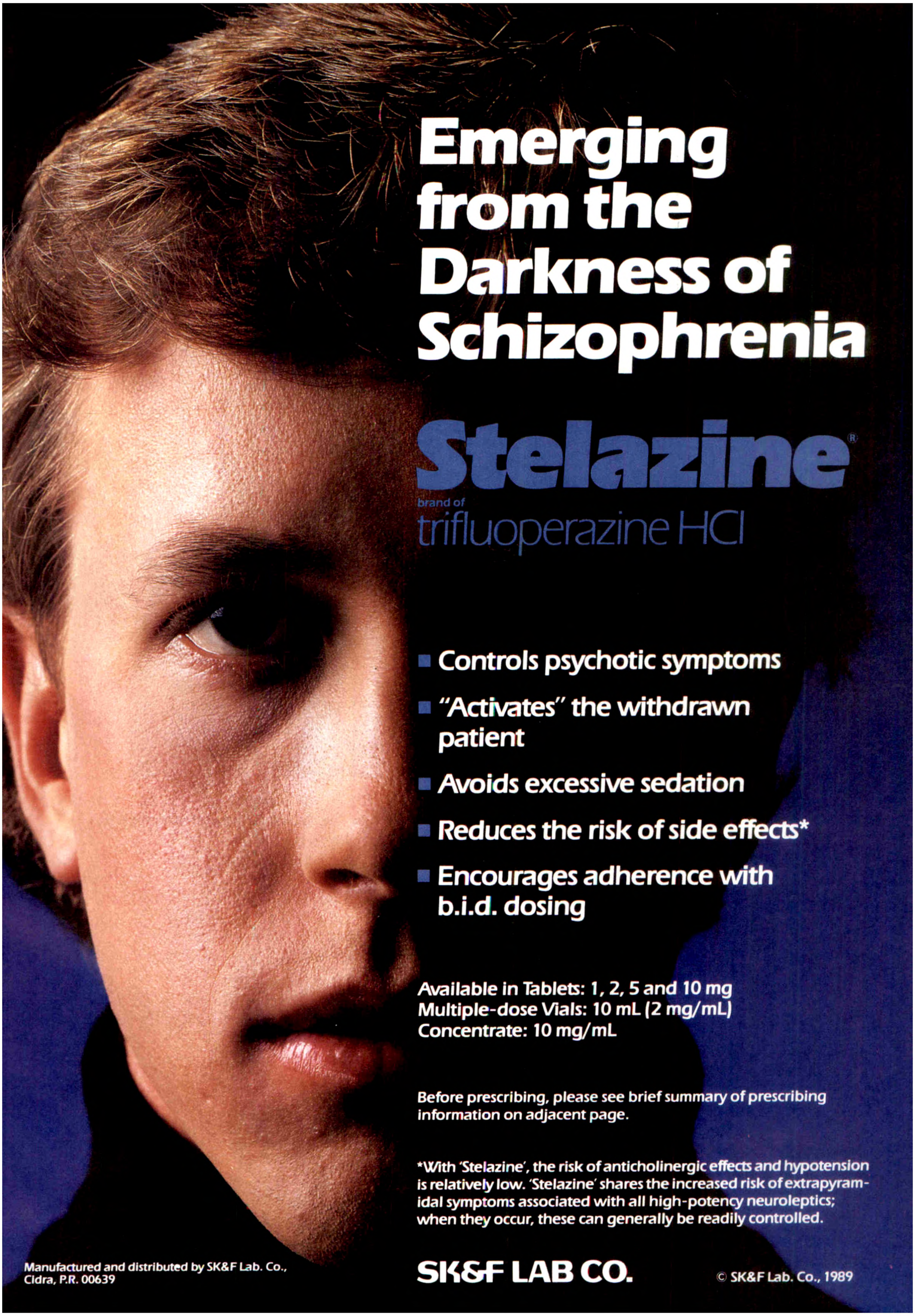

Emerging from the Darkness of Schizophrenia

Stelazine®

brand of
trifluoperazine HCl

- Controls psychotic symptoms
- "Activates" the withdrawn patient
- Avoids excessive sedation
- Reduces the risk of side effects*
- Encourages adherence with b.i.d. dosing

Available in Tablets: 1, 2, 5 and 10 mg
Multiple-dose Vials: 10 mL (2 mg/mL)
Concentrate: 10 mg/mL

Before prescribing, please see brief summary of prescribing information on adjacent page.

*With 'Stelazine', the risk of anticholinergic effects and hypotension is relatively low. 'Stelazine' shares the increased risk of extrapyramidal symptoms associated with all high-potency neuroleptics; when they occur, these can generally be readily controlled.

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Stelazine® brand of

trifluoperazine HCl

Before prescribing, see complete prescribing information in SK&F Lab Co. literature or PDR. The following is a brief summary.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations include: Hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment, if available, of any concomitant serious medical problems.

'Stelazine' Concentrate contains sodium bisulfite, which may cause allergic-type reactions including anaphylactic symptoms or asthmatic episodes in certain susceptible people. The prevalence of sulfite sensitivity in the general population is unknown and probably low and is seen more frequently in asthmatic than in non-asthmatic people.

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent in vitro, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecomastia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

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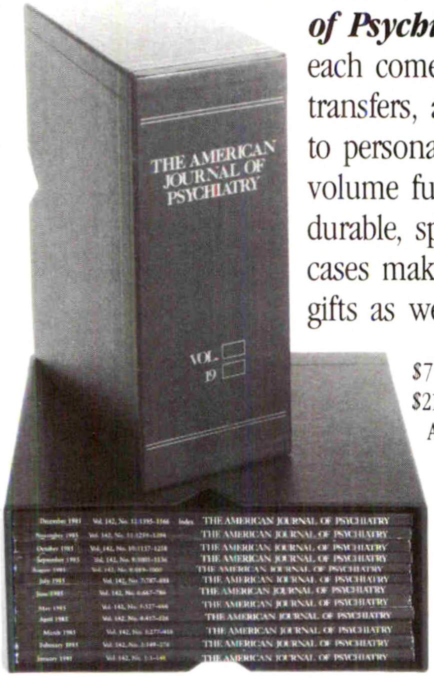

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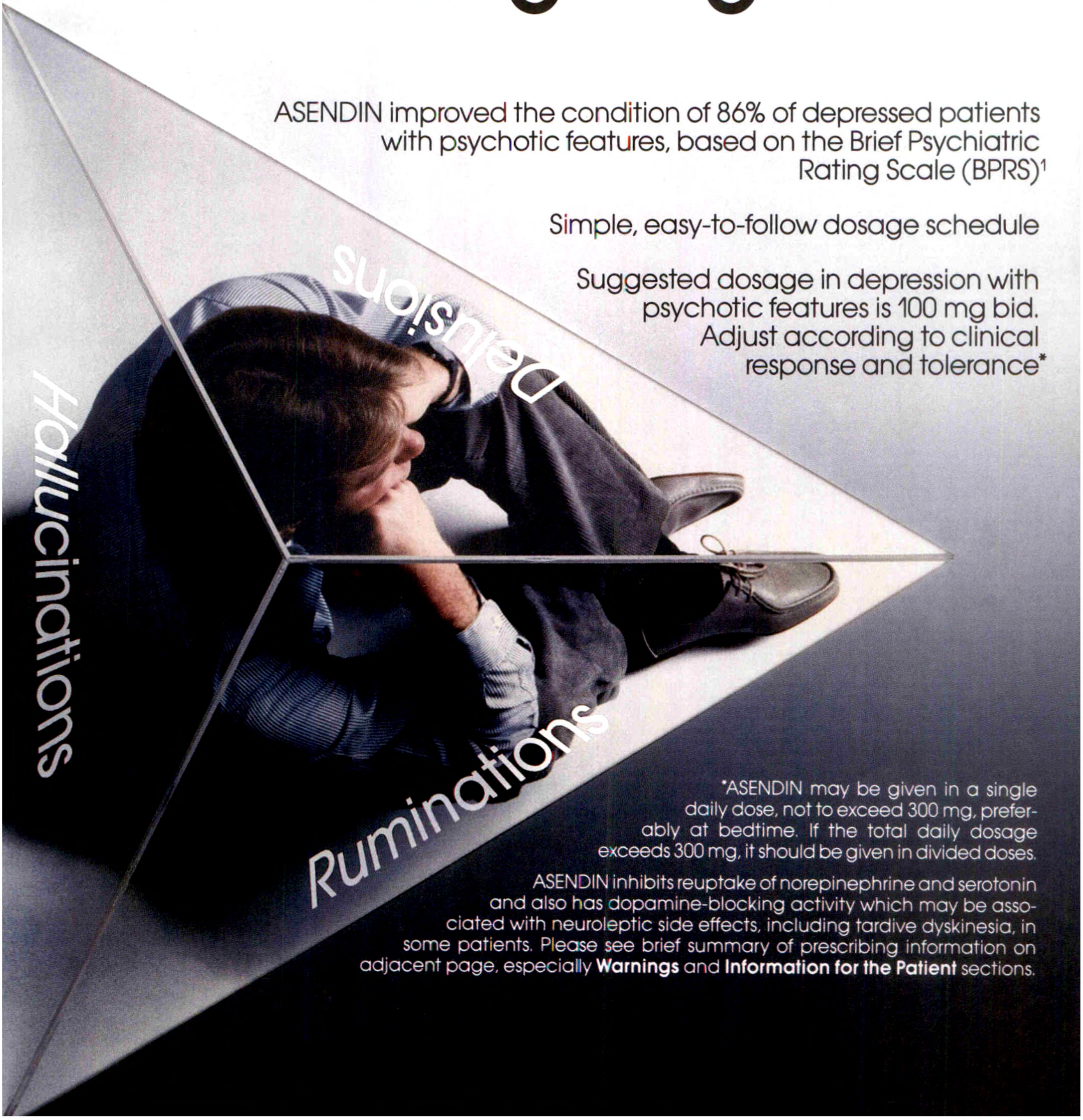

ASENDIN improved the condition of 86% of depressed patients with psychotic features, based on the Brief Psychiatric Rating Scale (BPRS)[1]

Simple, easy-to-follow dosage schedule

Suggested dosage in depression with psychotic features is 100 mg bid. Adjust according to clinical response and tolerance*

*ASENDIN may be given in a single daily dose, not to exceed 300 mg, preferably at bedtime. If the total daily dosage exceeds 300 mg, it should be given in divided doses.

ASENDIN inhibits reuptake of norepinephrine and serotonin and also has dopamine-blocking activity which may be associated with neuroleptic side effects, including tardive dyskinesia, in some patients. Please see brief summary of prescribing information on adjacent page, especially **Warnings** and **Information for the Patient** sections.

Brief Summary
ASENDIN® amoxapine Tablets
25 mg, 50 mg, 100 mg, 150 mg

CLINICAL PHARMACOLOGY

ASENDIN is an antidepressant with a mild sedative component to its action. The mechanism of its clinical action in man is not well understood. In animals, amoxapine reduced the uptake of norepinephrine and serotonin and blocked the response of dopamine receptors to dopamine. Amoxapine is not a monoamine oxidase inhibitor.

ASENDIN is absorbed rapidly and reaches peak blood levels approximately 90 minutes after ingestion. It is almost completely metabolized. The main route of excretion is the kidney. *In vitro* tests show that amoxapine binding to human serum is approximately 90%. In man, amoxapine serum concentration declines with a half-life of eight hours. However, the major metabolite, 8-hydroxyamoxapine, has a biologic half-life of 30 hours. Metabolites are excreted in the urine in conjugated form as glucuronides.

Clinical studies have demonstrated that ASENDIN has a more rapid onset of action than either amitriptyline or imipramine. The initial clinical effect may occur within four to seven days and occurs within 2 weeks in over 80% of responders.

INDICATIONS

ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions and depression accompanied by anxiety or agitation.

CONTRAINDICATIONS

Prior hypersensitivity to dibenzoxazepine compounds and in the acute recovery phase following myocardial infarction. Do not give concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. Before replacing a monoamine oxidase inhibitor with ASENDIN allow a minimum of 14 days to elapse, then initiate cautiously, with gradual increase in dosage until optimum response is achieved.

WARNINGS

Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (ie, antipsychotic) drugs. (Amoxapine is not an antipsychotic, but it has substantive neuroleptic activity.) Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on **Information for the Patient** and **ADVERSE REACTIONS.)**

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex, NMS has been reported in association with antipsychotic drugs. Clinical manifestations are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Diagnosis is complicated. Rule out serious medical illness (eg, pneumonia, systemic infection) and inadequately treated extrapyramidal symptoms (EPS). Other considerations in differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology. Management of NMS includes immediate discontinuation of antipsychotic and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of concomitant serious medical problems for which specific treatments are available. Reintroduction of antipsychotic drug treatment after recovery from NMS should be carefully considered and closely monitored since recurrences of NMS have been reported.

Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intraocular pressure. Watch patients with cardiovascular disorders closely. Tricyclic antidepressants, particularly in high doses, can induce sinus tachycardia, changes in conduction time, and arrhythmias. Myocardial infarction and stroke have been reported with drugs of this class. Take extreme caution in patients with history of convulsive disorders or those with overt or latent seizure disorders.

PRECAUTIONS

General: Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the drug. Manic depressive patients may experience a shift to the manic phase; schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have such symptoms exaggerated, requiring reduction of dosage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause skin rashes and/or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. ASENDIN *amoxapine* should be discontinued if rash and/or fever develop. Amoxapine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in <1% of patients. Rarely, symptoms indicative of tardive dyskinesia have been reported. **Information for the Patient:** It is advised that all patients in whom chronic use of neuroleptic drugs is contemplated be given full information about the risk of tardive dyskinesia. Warn patients of possibility of drowsiness; performance of potentially hazardous tasks such as driving an automobile or operating machinery may be impaired. **Drug Interactions:** See **CONTRAINDICATIONS** regarding concurrent usage of tricyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur when tricyclic antidepressants are taken in combination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when cimetidine is administered concurrently. Although such an interaction has not been reported to date with ASENDIN, specific interaction studies have not been done, and the possibility should be considered. **Therapeutic Interactions:** Concurrent administration with electroshock may increase hazards associated with such therapy. **Carcinogenesis, Impairment of Fertility:** In a 21-month toxicity study at three-dose levels in rats, pancreatic islet cell hyperplasia occurred with slightly increased incidence at doses 5-10 times the human dose. Pancreatic adenocarcinoma was detected in low incidence in the mid-dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length. **Pregnancy:** *Pregnancy Category C.* Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between days 0-4) was demonstrated in the offspring of rats at 5-10 times the human dose. There are no adequate and well-controlled studies of pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women. **Pediatric Use:** Safety and effectiveness in children below the age of 16 have not been established.

ADVERSE REACTIONS

Reported in Controlled Studies: **Incidence Greater than 1%:** Most frequent were sedative and anticholinergic: drowsiness (14%), dry mouth (14%), constipation (12%), and blurred vision (7%).

Less frequently reported reactions were: *CNS and Neuromuscular:* anxiety, insomnia, restlessness, nervousness, palpitations, tremors, confusion, excitement, nightmares, ataxia, alterations in EEG patterns. *Allergic:* edema, skin rash. *Endocrine:* elevation of prolactin levels. *Gastrointestinal:* nausea. *Other:* dizziness, headache, fatigue, weakness, excessive appetite, increased perspiration. **Incidence Less than 1%:** *Anticholinergic:* disturbances of accommodation, mydriasis, delayed micturition, urinary retention, nasal stuffiness. *Cardiovascular:* hypotension, hypertension, syncope, tachycardia. *Allergic:* drug fever, urticaria, photosensitization, pruritus, rarely, vasculitis, hepatitis. *CNS and Neuromuscular:* tingling, paresthesias of the extremities, tinnitus, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, extrapyramidal symptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported. (See **WARNINGS**.) *Hematologic:* leukopenia, agranulocytosis. *Gastrointestinal:* epigastric distress, vomiting, flatulence, abdominal pain, peculiar taste, diarrhea. *Endocrine:* increased or decreased libido, impotence, menstrual irregularity, breast enlargement, and galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion. *Other:* lacrimation, weight gain or loss, altered liver function, painful ejaculation. **Drug Relationship Unknown:** Reported rarely, but under circumstances where drug relationship was unknown: *Anticholinergic:* paralytic ileus. *Cardiovascular:* atrial arrhythmias (including atrial fibrillation), myocardial infarction, stroke, heart block. *CNS and Neuromuscular:* hallucinations. *Hematologic:* thrombocytopenia, eosinophilia, purpura, petechiae. *Gastrointestinal:* parotid swelling. *Endocrine:* change in blood glucose levels. *Other:* pancreatitis, hepatitis, jaundice, urinary frequency, testicular swelling, anorexia, alopecia. **Additional Adverse Reactions:** Reported with other antidepressant drugs, but not with ASENDIN. *Anticholinergic:* sublingual adenitis, dilation of the urinary tract. *CNS and Neuromuscular:* delusions. *Gastrointestinal:* stomatitis, black tongue. *Endocrine:* gynecomastia.

OVERDOSAGE

Signs and Symptoms: Toxic manifestations of ASENDIN overdosage differ significantly from those of other tricyclic antidepressants. Serious cardiovascular effects are seldom, if ever, observed. However, CNS effects — particularly grand mal convulsions — occur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitutes a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN overdosage in some cases. Renal failure may develop two to five days after toxic dosage, typically in those who have experienced multiple seizures. **Treatment:** Treatment of ASENDIN overdosage should be symptomatic and supportive but with special attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, requires vigorous treatment such as that described by Delgado-Escueta, et al (*N Engl J Med* 1982, 306:1337-1340).

Convulsions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant medication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for nondrug-induced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdosage, and the ECG typically remains within normal limits, except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is *not* a useful guide to the severity of overdosage with this drug. Fatalities and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENDIN overdosage patients.

Rev. 11/87

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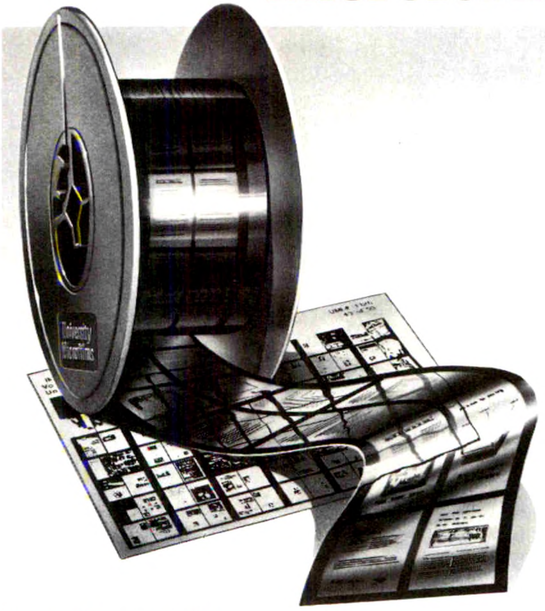

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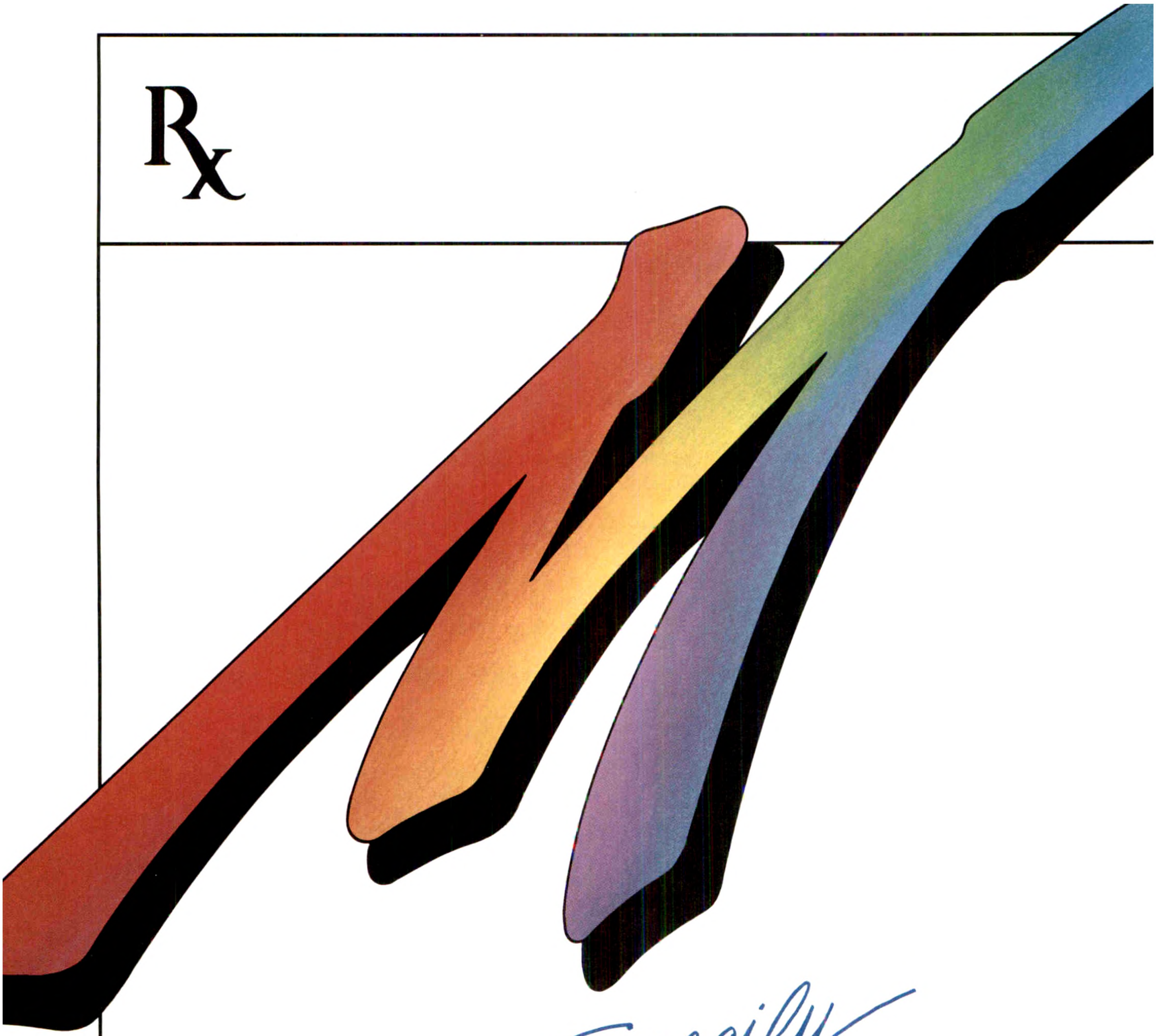

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THE AMERICAN JOURNAL OF PSYCHIATRY

Editorial

ECT for Parkinson's Disease

Parkinson's disease afflicts 1% of the population over age 50 (1)—there are a half-million sufferers in the United States alone—and two-thirds of those affected are severely disabled within 10 years of onset. The introduction of levodopa therapy has increased the life expectancy but not the ultimate prognosis of patients with this disorder, resulting in a higher prevalence of older, chronically disabled patients, many of whom are also resistant to or intolerant of drug therapy. Despite the great therapeutic benefits that it has conferred to many patients with Parkinson's disease, levodopa therapy is also associated with one of the most crippling manifestations of the disorder—the on-off syndrome. This syndrome is characterized by abrupt swings from marked relief of symptoms ("on") to total immobility ("off"), often occurring several times throughout one day.

Stereotactic surgery (e.g., chemopallidectomy), introduced in the 1950s for severe cases of Parkinson's disease, particularly those with predominantly unilateral features, was only occasionally effective and has been virtually abandoned since the advent of levodopa therapy. Recently, the hope of improved therapeutic results has been raised by the introduction of surgical procedures for transplanting autologous adrenal medullary tissues or fetal neural tissues into the caudate nuclei of patients with Parkinson's disease (2).

The first experimental surgical implant of fetal tissue into the brain of a patient with Parkinson's disease performed in the United States took 8 hours and cost $10,000 (3); its results may not be known for some time. A recently completed multicenter study of autologous adrenal medullary transplants for advanced Parkinson's disease (4), which required the combined efforts of a highly specialized team of neurological and general surgeons, movement disorder specialists, intensive and internal care physicians, and psychologists, failed to replicate the dramatic results reported earlier for this procedure from Mexico (5, 6). Medical complications were frequent: two patients suffered cerebrovascular accidents, 11 developed pneumonia, one became chronically depressed, and one lapsed into a coma and remained in a persistent vegetative state.

In contrast, in "ECT and Parkinson's Disease Revisited: A 'Naturalistic' Study" in this issue of the *Journal,* Richard Douyon, Michael Serby, Bruce Klutchko, and John Rotrosen report rapid improvement of motor symptoms—sustained for as long as 6 months—in several depressed patients with Parkinson's disease, using a safe, inexpensive, and widely available treatment: ECT. Their experience is neither unique nor new. Of 23 communications since 1953 describing results with ECT in more than 50 patients with Parkinson's disease—often, but not always, treated for coexisting depression or mania—all but two have been favorable. The most provocative of these was a 1985 abstract of a group of French investigators (7) reporting that four out of six patients with Parkinson's disease who had improved markedly after receiving ECT for coexisting depression showed no signs of Parkinson's disease 3–8 years later and had not required antiparkinsonian treatment during the follow-up interval. More compelling than these data reported in an abstract, however, is a recent double-blind, random-allocation comparison of genuine versus sham (placebo) ECT in nondepressed patients with Parkinson's disease with the on-off syndrome (8). This study found significantly longer "on" phases after the active treatment.

There is a theoretical basis for the salutary effects of ECT in patients with Parkinson's disease. Electrically induced seizures in rodents reliably increase dopamine-mediated behaviors (9); in man, there is a systematic fall in ECT-induced prolactin release over a course of treatments (10, 11). Together, these observations suggest that induced seizures increase dopamine receptor sensitivity, an effect with obvious implications for the relief of Parkinson's disease. Consistent with this hypothesis is Douyon and associates' observation that two patients, both of whom received maintenance combination doses of carbidopa and levodopa while they were receiving ECT, developed severe dyskinesias immediately after ECT was stopped; the dyskinesias disappeared when these patients' drug doses were halved.

Although four of Douyon and associates' patients remained improved 6 months after ECT, a more frequent observation is that ECT-induced amelioration of Parkinson's disease lasts for days or weeks. It is likely that the duration of symptomatic improvement can be prolonged through the use of maintenance ECT, a procedure used clinically to extend the period of remission in depressed patients who relapse rapidly after a successful course of ECT. In maintenance ECT, additional outpatient treatments are given after the initial hospital course at a frequency—generally biweekly to monthly—titrated to keep the patient free of symptoms. Brief-pulse, right-unilateral ECT—a method virtually devoid of undesirable effects on memory (12)—is ideal for this purpose. Indeed, it should have fewer cognitive side effects than levodopa or anticholinergics, both of which are capable of substantially interfering with memory functioning (13).

I therefore strongly agree with Max Fink's recent call for prospective controlled trials of ECT in the treatment of patients with intractable Parkinson's disease (14, 15). While awaiting the initiation and completion of such studies, however, I further recommend a therapeutic trial of ECT for every patient with intractable or drug-resistant Parkinson's disease, particularly those with the on-off syndrome. The morbid and mortal risks of such treatment are minimal, even in the presence of dementia (16), and minuscule compared with those of transplant surgery.

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Fifty Years After Freud: Dora, the Rat Man, and the Wolf-Man

Peter Buckley, M.B., Ch.B.

Three of Freud's case histories are reviewed and reexamined from the perspective of modern psychodynamic thinking. The Dora case illuminates advances in our understanding of adolescent psychology and countertransference. The cases of the Rat Man and the Wolf-Man draw attention to our increased awareness since Freud of the importance of the therapeutic relationship and the recognition that a two-person psychology is at work in the psychotherapeutic situation. The heuristic value of such comprehensive case reports is emphasized.

(Am J Psychiatry 1989; 146:1394–1403)

> No one who, like me, conjures up the most evil of those half-tamed demons that inhabit the human breast, and seeks to wrestle with them, can expect to come through the struggle unscathed.
>
> —Freud (1)

Fifty years after his death, Freud's case histories retain an enduring interest. Written in a masterful fashion that has never been surpassed in the psychodynamic literature, they form a complex tapestry of clinical data interwoven with theoretical formulations and expositions of psychotherapeutic technique. The three major clinical accounts of analyses personally conducted by Freud are vivid portrayals not only of the patients but of Freud at work. They provide a window into the consulting room of the pioneer of psychodynamic psychotherapy as he struggles with the "demons that inhabit the human breast."

Interest in the case histories has extended outside the clinical sphere. The literary critic Steven Marcus has analyzed the Dora case as a piece of writing and concluded that Freud's account is a great work of modernist literature: "an outstanding creative and imaginative performance and an intellectual and cognitive achievement of the highest order" (2). He has suggested that the content and form of the Dora case are analogous to Ibsen's plays, but with one major difference—Freud is not only the creator of the work, he is also one of the characters in the action who suffers as much as anyone.

Beyond their historical and literary importance, the case histories illustrate the evolution of Freud's psychodynamic theory and practice, and they create a striking background against which current theoretical developments and insights into the clinical psychotherapeutic situation can be contrasted. Eissler has called Freud's case histories "the pillars upon which psychoanalysis as an empirical science rests" (3, p. 395). It is the intention of this paper to reexamine three of those pillars, Dora, the Rat Man, and the Wolf-Man, in the light of modern psychodynamic thinking and to draw attention to the heuristic value of such comprehensive case reports in an age, as Peter Gay (4) has commented, that seems to have forgotten how to write them.

DORA

In October 1900, Freud wrote to Fliess, his colleague and confidant: "It has been a lively time, and I have a new patient, a girl of eighteen; the case has opened smoothly to my collection of picklocks" (5, p. 325). This patient was destined to become famous as Dora when Freud published in 1905 his "Fragment of

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an Analysis of a Case of Hysteria" (1), the first of his major case studies. Dora's analysis came to an end after 3 months when she abruptly broke off the treatment, an action that shook Freud but led him to his epochal recognition of the centrality of transference in all psychotherapeutic ventures.

More than any other of Freud's case histories, Dora has generated a plethora of criticism, comment, and reanalysis since its original publication. In part, this can be viewed as a consequence of Freud's expository and literary skill, which lends his account a compelling narrative thrust while simultaneously providing a wealth of clinical material concerning Dora and the unfolding of the treatment. Freud's questionable technique has stimulated considerable retrospective comment by clinicians, as has his countertransference to Dora. Social historians and feminist scholars (6, 7) have found much to interest them in the Dora case concerning aspects of male-female relations in late nineteenth-century Vienna, where hysteria in women appeared to flourish. Jennings (8) has suggested that the efflorescence of papers on Dora during the past two decades has been catalyzed by the development of more sophisticated theories of countertransference and adolescent psychology, which lead to a better understanding of why the treatment failed than the reasons provided by Freud.

Freud had successfully treated Dora's father, a well-to-do manufacturer, for syphilis when Dora was 10. Dora's father brought her to Freud for a consultation when she was 16. According to Freud (1), she was at that time "unmistakeably neurotic," but she balked at his recommendation that she enter treatment. Two years later, Freud significantly noted that her father "handed her over to me for psychotherapeutic treatment." Ostensibly, the discovery of a note written by Dora threatening suicide, followed by a fainting spell after an argument with her father, led him to insist on her entering treatment with Freud despite her reluctance. As was to emerge, Dora rightly felt that her father had an ulterior motive in mandating her treatment.

Freud noted that Dora had developed chronic psychogenic dyspnea at age 8. At 12 she developed migraine and tussis nervosa. The latter symptom persisted and was present, accompanied by recurrent aphonia, when Freud took her into treatment. Simultaneously she exhibited social withdrawal, fatigue, lack of concentration, and, in Freud's words, "chronically low spirits," a symptom picture consistent with depression.

Freud presented the case as further confirmation of his thesis, outlined in "Studies on Hysteria" (9), that the psychological determinants of hysteria lie with "a psychical trauma, a conflict of affect, and—an additional factor . . .—a disturbance in the sphere of sexuality." In Dora's case these determinants were to be found in the sexual entanglements in which Dora found herself involving her father and intimate friends of her parents, Herr and Frau K. Dora's father was miserable in his marriage and was embroiled in an affair with Frau K, while Herr K had made sexual advances to Dora when she was 16 during a vacation the two families spent together. Dora informed her parents of Herr K's impropriety and they confronted Herr K, but he denied the episode and ascribed it to a fantasy arising out of Dora's preoccupation with sexual matters, something he had been apprised of by his wife. Dora's father confided in Freud that he agreed with Herr K that Dora was in the grip of an irrational fantasy, denied that he was having an affair with Frau K, and asserted that there was nothing to his daughter's allegations.

Freud, ever the shrewd skeptic, did not swallow Dora's father's protestations of innocence. He uncovered an earlier episode of attempted seduction of Dora by Herr K when she was 14. Dora was convinced that "she had been handed over to Herr K as the price of his tolerating the relations between her father and his wife" (1), thus justifying her rage at her father. Freud, however, observed that for some years before Herr K's attempt to kiss her when she was 16, Dora had actively colluded in facilitating the affair between her father and Frau K. Freud concluded that Dora had actually been in love with Herr K during that time and suggested that her fury at her father for his affair was fueled by her oedipal feelings, which had been aroused to defend her against conflict created by the intensity of her feelings for Herr K. Freud interpreted that Dora wanted Herr K to continue his entreaties and marry her and that she was horrified by his denial of the kissing episode at age 16 and his slandering her, thus fueling her fury at unfaithful men. Freud further elucidated that Dora and Frau K had been on the most intimate terms, had shared a bedroom together, and that unconsciously Dora had been in love with Frau K. Again, she had been betrayed when Frau K calumniated her to Dora's father and revealed their discussion of sexual topics.

The convoluted aspects of who was sexually involved with whom in this case are astonishing, indeed, and Marcus has a point in his statement that "in some sense everyone was conspiring to conceal what was going on; and in some yet further sense everyone was conspiring to deny that anything was going on at all. What we have here, on one of its sides, is a classical Victorian domestic drama that is at the same time a sexual and emotional can of worms" (2). Running through the case history is a constant theme of betrayal, manifest in Dora's feeling that she was never loved for herself but was constantly used, a conviction that was to reappear in her therapeutic relationship with Freud.

In publishing the case of Dora, Freud had two didactic purposes in mind, namely, to explicate the etiology of hysteria and to demonstrate the utility of his dream theory in clinical work. Two dreams and their painstaking analysis form the centerpiece of the report. The Dora case thus looks backward to *The Interpretation of Dreams* (10) and, in its exploration of the origins of hysteria, forward to the "Three Essays on the Theory of Sexuality" (11). Beyond these aspects, however, Freud provided in his retrospective review of the case the first clear clinical demonstration of transference, a discovery that was destined to revolutionize psychotherapeutic technique. He acknowledged that his failure to recognize and address the transference was central to Dora's abrupt termination, although he felt that his failure to interpret Dora's homosexuality —her attraction to Frau K—was a graver technical error, a position that would not be held today.

Gill and Muslin (12) have suggested that transference and resistances are always present and should be interpreted at all stages of an analytic treatment. In their opinion, a failure to do this leads to a premature interruption, as occurred with Dora. In a detailed study of the case report (13), they delineated the ubiquity of transference material unrecognized by Freud. An example of this can been seen in Dora's reproach against her father that she had been handed over to Herr K so that Herr K would tolerate the affair between her father and Herr K's wife. Gill and Muslin pointed out that there was a clear transference reproach concealed behind this, for Dora's father had supported her treatment with Freud for his own ulterior purposes, and hence she had also been "handed over" to Freud.

Gill and Muslin also provided evidence for Freud's intense countertransference to Dora, most notably his response to her returning of her own volition, asking for further help, 15 months after she broke off treatment. Freud wrote (1), "one glance at her face, however, was enough to tell me that she was not in earnest over her request." As Gill and Muslin pointed out, it is incredible that he could have known this from one glance at her face. That Freud felt he was a victim of Dora's underlying craving for revenge against men is clear from his transcript, but he failed to recognize his own hostility toward this rebellious patient. He stated (1), "I do not know what kind of help she wanted from me, but I promised to forgive her for having deprived me of the satisfaction of affording her a far more radical cure for her troubles." There is evidence that the name that he chose to call his patient in the report was derived from that of his sister's maidservant. When Dora announced to Freud that she would not come again and that she had decided this 2 weeks before telling him, he replied (1), "that sounds like a maidservant or governess—a fortnight's warning." Rogow (14) speculates that in calling his patient Dora after his sister's maid, Freud may have been expressing anger as well as resentment at her abrupt termination. In essence, she had behaved like a maidservant and would be called after one.

Another reason the case goes awry revolves around Freud's single-minded scientific quest with regard to the analysis of Dora's two dreams, whose understanding he felt would uncover the origins and meaning of her conversion symptoms. Erikson (15) has observed that Freud's method of working was strongly influenced by his first professional identity as a physiological researcher and that at the time, "his clinical method was conceived of as an analogy to clear and exact laboratory work." Dora again felt that she was being used for an ulterior purpose, in this case Freud's scientific explorations, just as the referral to Freud by her father was, in part, an attempt to buy her silence concerning the tortuous and convoluted secrets of who was sexually involved with whom. Even when Dora dramatically announced that she had come for her last session, Freud, apparently nonplussed, insisted on continuing, in his "scientific" way, with the analysis of her second dream, rather than immediately addressing the threat to the integrity of the treatment, as would be standard practice today.

The fact that Dora was an adolescent, with all its attendant developmental considerations, was ignored by Freud, who treated her as an "experienced," mature woman. In the course of her treatment, one sexual interpretation followed another with breathtaking speed in a manner that must have been overwhelming to Dora. Freud's "picklock" metaphor in his letter to Fliess seems apt, indeed, as libidinal interpretations were thrust upon her. Blos has commented,

> As we consider Dora's disruption of her analysis in developmental terms, we could say, today, that the consolidation of her neurotic condition had been short-circuited by the fact that her analysis was being conducted as if an adult neurosis already existed. As a consequence, the adolescent ego became overwhelmed by interpretations it was unable to integrate, and it simply took to flight. If there is one thing adolescent analysis has taught us, it is that ill-timed id interpretations are unconsciously experienced by the adolescent as a parental—that is, incestuous—seduction. (16)

While Dora, with her multiple symptoms, needed individual psychotherapy, in many ways she represents a classic case of the symptom carrier for the whole family. The sexual intrigue involving her father and the K family, the disavowal by everyone around her of the sexual subterfuge to which she was subjected, and the disruption of her adolescence by her immersion in this intrigue give the case, by today's standards, indications for concurrent family therapy. Such a therapy would address the secrets and dissimulation in which Dora's father participated and help to validate her reality, something Dora spontaneously did herself when she confronted her father and Herr K after she broke off her treatment with Freud.

Given that Dora was a late adolescent, a modern therapist would be far more circumspect than Freud about making constant sexual interpretations, which inevitably provide stimuli that sexualize and inflame the transference. Recognizing that Dora did not possess a mature ego and was part of a convoluted and pathogenic reality would ensure that the therapeutic stance was far more empathic than that which Freud displayed. The follow-up by Deutsch (17), with its vitriolic and far from objective description of Dora in middle-life (he called her "one of the most repulsive hysterics" he had ever met), suggests that she had a remarkable capacity for eliciting powerful negative responses from clinicians. Today such a reaction in the therapist would be seen as part of the clinical data that would help to illuminate her psychopathology; this view would be based on the current opinion that the emotional responses of the clinician to the patient are a potential source of insight into the patient's unconscious conflicts and defenses.

Freud's response to Dora, his outrage at her for sabotaging his therapeutic quest, his desire for cure, and his refusal to further treat her when she reappeared are startling, indeed. Nonetheless, one mark of Freud's greatness was his intense interest in cases that failed, and his publication of this failed case is a testimony to his intellectual honesty and to his assertion that one gains knowledge from such cases. Such publication and subsequent reexamination hastened the progress of psychoanalysis and psychotherapy and belies Gay's wry comment that "what is astonishing about the case history of Dora is . . . that he published it at all" (4, p. 255).

THE RAT MAN

Freud's treatment of Ernst Lanzer, a 29-year-old lawyer, who was to become known as the Rat Man, began in October 1907 and lasted 11 months. Freud discussed the case while it was in progress at the Vienna Psychoanalytic Society and stated during one of these meetings: "In general a human being cannot bear opposed extremes in juxtaposition, be they in his personality or in his reactions. It is this endeavor for unification that we call character. In regard to persons near to us extremely opposed emotions may be so strong as to become completely unbearable" (18, p. 263).

This comment goes straight to the heart of the case and Freud's didactic purpose in publishing it: the elucidation of the nature and meaning of obsessional symptoms. Freud published the finished report under the title "Notes Upon a Case of Obsessional Neurosis" in 1909 (19), but it is fortunate that his daily rough notes on the first 4 months of the treatment survived. They provide a unique entree into his day-to-day method of working, amplify aspects of the formal case report, and, as in the case of Dora, raise questions concerning his technique.

Lanzer consulted Freud complaining of obsessional thoughts that something might happen to his father and to a woman he loved, combined with a frightening impulse to cut his throat. From the beginning, Lanzer emphasized his sexual life, an early manifestation of the transference, as he assumed, on the basis of his fragmentary knowledge of Freud's theories, that this would interest Freud the most. Lanzer described the presence of a full-blown obsessional neurosis when he was 6 years old, which Freud viewed as the nucleus and prototype of the later disorder. Lanzer had the conviction that his parents could read his thoughts, such as his intense desire to see certain girls naked. Simultaneously he had "an uncanny feeling, as though something might happen if I thought such things, and as though I must do all sorts of things to prevent it" (19). His main fear as a child was that his father might die; this was the same fear he had when he entered treatment with Freud. At this point, to Freud's amazement, he learned that Lanzer's father had died several years previously.

In the second session Lanzer went on to describe the experience that had precipitated his consulting Freud. While he was on army maneuvers (Lanzer was in the Austrian military reserve), another officer recounted a horrible punishment used in the East. At this point, agitated, Lanzer broke off, got up from the couch, and begged Freud to spare him the recital of the details. Freud insisted that he continue. Lanzer described the punishment: "the criminal was tied up . . . a pot was turned upside down on his buttocks . . . some rats were put into it . . . and they bored their way in . . . " "Into his anus," Freud finished for him. It then emerged that Lanzer feared that both the woman whom he loved and his father were being subjected to this hideous torture, even though his father was long dead.

Lanzer's absence from his father's bedside when his father died had sent him into a paroxysm of guilt manifest in the conviction that he was a criminal. Freud interpreted to Lanzer that the affect was justified but that the sense of guilt belonged to an unconscious content of infantile origin, a murderous impulse toward his father. As if to mitigate the impact of this interpretation, Freud then delivered a brief didactic lecture to the patient on the psychological differences between the conscious and unconscious and concluded the session in a further supportive manner by saying "a word or two upon the good opinion I had formed of him, and thus gave him visible pleasure"; this was clearly a departure from the admonitions of abstinence that he later asserted in his papers on technique.

In his explication of the origins of Lanzer's suicidal impulses, Freud highlighted the centrality of aggression in obsessional neurosis. Unconscious rage directed at individuals who unwittingly thwarted Lanzer's wishes evoked a talion response—"kill yourself"—as punishment for this murderous passion, and it was this component of the process that passed into his consciousness. The battle between love and hate directed at the same object became represented in compulsive acts of doing and undoing on Lanzer's part.

As Freud attempted to uncover the origins of Lanzer's obsessional thoughts concerning the rat torture, memories of a childhood beating by his father surfaced. This was followed by a sudden eruption of fury directed at Freud: "he began heaping the grossest and filthiest abuse upon me and my family." Significantly, these outbursts would be followed by self-reproaches and Lanzer's leaping up from the couch and roaming about Freud's consulting room, fearing (and wishing) that Freud would give him a beating for his vile words, thus recapitulating his experience with his father. These events and associations led Freud to a solution of the rat idea. Hearing of this punishment had stimulated Lanzer's anal eroticism, and in an explanatory tour de force, Freud interwove aspects of the rat obsession with elements of Lanzer's recent and early life, with his childhood experience and fantasies, with his intense ambivalence toward his father, and, finally, with the symbolic meanings of rats. In a compelling argument he came to the denouement that Lanzer himself "had been (as a child) just such a nasty wretch, who was apt to bite people when he was in a rage, and had been fearfully punished for doing so. He could truly be said to find a living likeness of himself in the rat." Meticulously, Freud interpreted to Lanzer the unconscious meaning of the various elements of his obsessional symptoms, and, with remarkable dispatch, "when we reached the solution that has been described above, the patient's rat delirium disappeared."

In the formal transcript of the case Freud is still intent, like the conscientious archaeologist with whom he liked to compare himself, in detailed uncovering of the underlying origins and meaning of Lanzer's bizarre symptoms. (A similar approach was central to the thrust of his work with Dora, where, for example, her psychogenic cough and aphonia were traced to a fantasy of fellatio stimulated by her contact through her clothes with Herr K's erection when he attempted to seduce her.) At this stage, it was this meticulous "uncovering" of repressed memories that Freud believed was the primary therapeutic component of analysis.

In the cases of both Dora and the Rat Man, the importance of the mother-child relationship gets short shrift. Dora's mother is dismissed in a brief paragraph, while Lanzer's mother is incidentally referred to on only a few occasions, as if she were of little import. When one turns to the original notes on the case, however, a different picture emerges. After Lanzer's initial consultation with Freud and his being informed of the terms of the treatment, Freud recorded that Lanzer said he must consult his mother. The next day, after doing so, he came back and told Freud that he accepted them. Lanzer's mother's control over his life was further revealed by the fact that his inheritance from his father was in her hands and she doled out small amounts of money to her son at her discretion. Freud thus gives ample evidence of the importance of Lanzer's relationship with his mother in these rough notes, yet the significance of such material is not acknowledged in the formal report.

Lanzer gave expression to powerful feelings of aggression toward Freud during the treatment. At one point Freud noted, "he developed great irritation with me—he accused me of picking my nose, refused to shake hands with me, thought that a filthy swine like me needed to be taught manners and considered that the postcard I had sent him, and had signed 'cordially' was too intimate." For all this negative transference, as the sending of the postcard indicates, Freud maintained a strongly positive, even affectionate feeling toward Lanzer. On one occasion Freud noted, "He was hungry and was fed." This positive feeling of Freud's, coupled with solicitous actions such as literally feeding his patient, leads one to speculate that this therapeutic stance had a significant influence on Lanzer's symptomatic cure.

As Zetzel (20) has noted, Freud emphasized oedipal content in his interpretations, but anal-sadistic elements in Lanzer's basic conflict abound, particularly in the case notes in which the patient's preoccupations with buttocks, feces, and fantasies of torture are ubiquitous. In addition, Zetzel drew attention to the importance of the loss of an older sister, who died when Lanzer was 4, and highlighted his identification with his mother, which, Zetzel suggested, led Lanzer to relate to his father in an unconsciously homosexual and masochistic fashion.

Freud's technique in this case has received considerable criticism by later psychoanalysts, although Zetzel has defended Freud's departures from standard analytic technique as necessary for establishing a sturdy therapeutic alliance and suggested that Lanzer's identification with Freud, a father surrogate, may have been the central factor that enabled him to resolve his intrapsychic conflicts. Kanzer (21) observed that the case represents an early phase of psychoanalytic theory and technique redolent with the conspicuous intellectual indoctrination that prevailed at that time, when the importance of reliving in the transference was not yet emphasized. Kanzer felt that Freud, in supplying Lanzer with the words "into his anus," which Lanzer was unable to say while recounting the nature of the Eastern torture, was being seduced into the role not only of the cruel officer but also of the invading rats themselves. Muslin (22) has demonstrated that in this case, understanding of the use of the transference was in transition. Transference, while acknowledged, as it was not with Dora, was of importance in establishing conviction of the validity of repressed memories. The curative aspects of the unfolding and resolution of the transference neurosis, the sine qua non of modern-day psychoanalysis and insight-oriented psychotherapy, were not yet recognized.

Lipton (23) has taken issue with those who have suggested that Freud's technique with Lanzer was only a precursor of his later "classical" technique. He marshaled evidence to show that Freud's technique did not change after the analysis of Lanzer, and the later conduct of the Wolf-Man case would tend to confirm this thesis. The question of Freud's relationship with the patient and its existing outside formal technique is at issue. Lipton argued that modern technique, with its emphasis on neutrality, has been expanded to cover the personal relationship that develops between patient and therapist but that there are dangers inherent in this, namely, that the systematic attempt to obliterate any personal influence may hinder the development of an object relationship. In Lipton's view Freud's technique existed separate from the personal relationship between him and Lanzer, and his recognition of their separateness fostered the establishment of an object relationship that enhanced the course of the analysis.

Tragically, Lanzer died in World War I, so that long-term clinical follow-up is lacking, although Freud noted in a letter to Jung in 1909 that Lanzer had announced his engagement and was "facing life with courage and ability" (24, pp. 157, 158). Theoretical developments since Freud, particularly those exemplified by the object relations school, would lead to the contention that the impressive therapeutic effects that were obtained resulted as much from Lanzer's positive object relationship with Freud and its internalization as from interpretive work alone. The case of the Rat Man and its remarkable therapeutic results highlight the question of the nature of therapeutic action, an issue that remains controversial in dynamic psychotherapy and psychoanalysis to this day.

THE WOLF-MAN

The case history of the Wolf-Man, as Strachey has noted (25), is the most elaborate and, in Freud's eyes, the most important of his clinical accounts. Still rankled by the defections of Jung and Adler and their criticisms and dilution of his view of the crucial importance of infantile sexuality in normal development and psychopathology, Freud published "From the History of an Infantile Neurosis" (26) in 1918 with the frank polemical intent of refuting their claims and providing convincing proof of his own. The availability of accounts of the subsequent treatment of the Wolf-Man after his analysis with Freud, together with the patient's autobiography, adds a further dimension to our understanding of this patient.

By the time Sergei Pankejeff, a wealthy Russian aristocrat, came to Freud for treatment in 1910 at the age of 23, he had become a psychological invalid crippled by multiple phobias and anxieties and was unable even to dress himself. He had already consulted some of the leading psychiatrists of the day, including Emil Kraepelin, seeking relief from his condition but to no avail. His treatment lasted 4 years, at which point Freud regarded the case as completed, although subsequent events were to show that this was overly optimistic. Ernest Jones (18) has revealed that Pankejeff initiated the first hour with the offer to have rectal intercourse with Freud and then to defecate on his head! Such a beginning would give the modern psychotherapist pause, to say the least, and raise immediate questions concerning the gravity of the patient's psychopathology and psychoanalysis as the treatment of choice.

Freud began his account by noting that Pankejeff developed an animal phobia immediately before his fourth birthday and that this was followed by an obsessional neurosis that lasted into his tenth year. This infantile neurosis, analyzed some 15 years later, is the main subject of Freud's communication. He acknowledged that his abstaining from writing a complete account of Pankejeff's adult illness, treatment, and recovery, on the grounds that such a task was technically impractical and would breach confidentiality, prevented him from demonstrating the connection between the childhood condition and the adult illness; however, he leaves no doubt in the reader's mind of his conviction that this connection is essential to an understanding of the adult condition.

Pankejeff was the younger child, born on Christmas Day, of a wealthy landowning Russian family. At the age of three and one-half, a sudden transformation occurred in his character. Formerly good-natured and agreeable, he suddenly became "discontented, unstable and violent, took offense on every possible occasion, and then flew into a rage" (26). Shortly thereafter he became terrified of a picture of a wolf in a book, which his older sister proceeded to use to torment him. Other fears of insects and horses emerged, although he recalled that simultaneously he liked to torture beetles, cut caterpillars into pieces, and beat horses. At the age of 8, he developed an obsessional neurosis, marked by religious content, that involved an identification with Christ, with whom he shared his birthday.

Freud elicited from his patient childhood memories of sexual seduction by his sister and a threat of castration from his nursemaid in response to masturbatory exhibitionism. Freud saw this arousal of castration anxiety as leading to a regression to a pregenital anal-sadistic organization that manifested itself in his childhood predeliction for torturing insects and animals. Freud postulated that Pankejeff's seduction by his sister had forced him into a passive role and given him a passive sexual aim, particularly toward his father. His outbursts of rage thus had a masochistic intent, designed to elicit beatings from his father.

The *pièce de résistance* of Freud's account is his analysis of Pankejeff's anxiety dream of childhood in which he saw six or seven wolves sitting on a tree outside his bedroom window, a scene that terrified him and woke him up. This dream was to provide the case with its informal title and the pseudonym that was adopted by the patient in his autobiography. (Later in life, when Pankejeff had settled into the role of being Freud's most famous patient, he would paint pictures of this dream and give them to visiting psychoanalysts.) With his typical expository skill, Freud argued that the dream represented the child's transformation of being a witness to his parents' sexual intercourse. The pathogenic effect of this primal scene and the repudiation of his wish for sexual satisfaction from his father, with its implication of castration, resulted in the appearance of the wolf phobia. Freud concluded that this primal scene experience took place during Pankejeff's infancy, and he marshaled his considerable persuasive skills to convince the skeptical reader of this reconstruction. However, the reality of this event, as opposed to a later primal scene fantasy, remains controversial.

In analyzing the childhood obsessional neurosis, Freud delineated three sexual trends directed by Pankejeff toward his father: "from the time of the dream onwards, in his unconscious he was homosexual, and in his neurosis he was at the level of cannibalism; while the earlier masochistic attitude remained the dominant one." The cannibalistic or oral phase of libido delineated by Freud was to play a central role in his later theories of incorporation, identification, and the origins of depression. Pankejeff's religious preoccupations, doubts, fears, and ambivalence were seen as being unconsciously directed toward his father. Freud viewed Pankejeff's lack of interest in the world at large during his analysis as a consequence of his repression of his overpowerful homosexuality; however, given the family history of affective illness (both Pankejeff's father and sister committed suicide), one wonders if he was not suffering from a concomitant depressive illness.

One of Pankejeff's multitude of complaints was of a severe, intractable constipation. Freud observed how doubt is the obsessional patient's "strongest weapon, the favorite expedient of his resistance." This doubt had served to keep Pankejeff's response to the treatment negligible in terms of therapeutic results. Freud seized on the intestinal symptom as representing "the small trait of hysteria which is regularly to be found at the root of an obsessional neurosis." He promised him a return to normal bowel activity. In the face of Pankejeff's incredulity, Freud then had "the satisfaction of seeing his doubt dwindle away, as in the course of the work his bowel began, like a hysterically affected organ, to 'join in the conversation,' and in a few weeks' time recovered its normal function." Freud had spent some time analyzing Pankejeff's anal eroticism and its relationship to his feminine identification and castration anxiety and postulated that the regular enemas he received for his constipation had the symbolic meaning of copulation. Freud believed that this interpretive work resulted in the disappearance of the symptom, but the frank suggestive element in his asserting to Pankejeff that the symptom would disappear is apparent.

In Freud's view, Pankejeff's breakdown had been precipitated by his contracting gonorrhea, which carried the unconscious meaning of castration. In his infantile neurosis, the wolf phobia had broken out when he was faced with the reality that such a thing as castration was possible. It was through the unveiling of the primal scene, the uncovering of his identification with his mother, and the wish to be sexually satisfied by his father and to present him with an anal child that Freud believed the case to be resolved. The focus was thus upon the negative oedipus complex. More primitive preoedipal conflicts, particularly those involving separation, were seen as less important, and, as in the cases of Dora and the Rat Man, the mother-child relationship remained in the background.

In his introductory remarks, Freud reveals that there was no movement in this case until he set a specific termination date and hence a specific time limit on the treatment. This radical (and coercive) technical maneuver resulted in the appearance of all the material that Freud recounted concerning the infantile neurosis and allowed the treatment to advance to the point where Pankejeff's symptoms temporarily remitted. Meissner (27) has suggested that the breakthrough of resistances and flood of material that appeared as a consequence of this maneuver represented just another level of compliant submission by Pankejeff to Freud's insistence.

Offenkrantz and Tobin (28) have observed that Pankejeff was of particular interest to Freud because of his unique role in the development of the theory of infantile sexuality. Freud thus had a research interest in Pankejeff that made him more than just another patient. In support of this, Jones (18) has noted that when Pankejeff returned for a brief period of treatment in 1919 after the Russian revolution had swept away his fortune, Freud treated him without fee and collected money to sustain him and his wife for some 6 years. Offenkrantz and Tobin raised the possibility that the day residue for the six wolves in the manifest content of the wolf dream at the time it was first reported was a photograph in Freud's consulting room of the six psychoanalysts who were his early colleagues. In this regard, they observed that the transference implications of the dream are absent from Freud's report. They postulated that Pankejeff was extremely interested in and sensitive to the two roles that Freud was playing simultaneously, both therapist and investigator. In a further study of the problems of conducting an analysis with simultaneous therapeutic and research goals (29), they suggested that such a dual function stimulates primal scene fantasies.

Freud's second treatment of Pankejeff in 1919 lasted 4 months and dealt successfully with "a piece of transference which had not hitherto been overcome," whose nature is not elaborated on by Freud (26). In 1926, Pankejeff again consulted Freud and was referred on this occasion to one of Freud's pupils, Ruth Mack Brunswick, who subsequently published an account of her 5-month treatment (30). Significantly, Brunswick's therapy was conducted without fee, which must have further confirmed Pankejeff's view of himself as a special patient.

When he came to Brunswick, Pankejeff had decompensated alarmingly and had developed a delusional paranoid psychosis with hypochondriacal features. He was convinced that he possessed a gaping hole in his nose as a consequence of the treatment of an obstructed nasal sebaceous gland by electrolysis. He was obsessed with this and felt unable to go on living in what he viewed as his irreparably mutilated state. He had formed a delusional hatred toward the physician who had treated him, although it soon became apparent that this was a substitute for Freud, whom he blamed for the loss of his fortune in Russia. Simultaneously, Pankejeff maintained (not without cause) that he had a special, favored relationship with Freud.

Brunswick attacked Pankejeff's view of himself as Freud's favorite son, which today we would view as an assault on the patient's narcissistic defenses. It emerged that Pankejeff's decompensation had been precipitated by his learning of Freud's life-threatening illness, the cancer of the palate that was ultimately to prove fatal. Meissner (27), reviewing the case from the perspective of Kohut's self psychology, postulated that Freud had served as an idealized self-object with whom Pankejeff had developed an idealizing narcissistic transference and that his psychological equilibrium was gravely threatened by Freud's illness.

Brunswick focused on interpreting Pankejeff's castration anxiety and death wishes toward his father and Freud. In the midst of this Pankejeff became more floridly psychotic: "He talked wildly in terms of his fantasies, completely cut off from reality. He threatened to shoot both Freud and me . . . and somehow these threats sounded less empty than those which one is accustomed to hear" (30). Following a dream in which Brunswick appeared as his mother, who destroys religion and frees him from his identification with the suffering Christ, Pankejeff's psychotic state remitted with surprising rapidity. Meissner (27) suggested that this rapid recovery was a consequence of the formation of a new narcissistic object relationship with Brunswick, accompanied by fantasies of protective omnipotence to replace the threatened loss of the idealized self-object, whom Freud represented.

From the vantage point of present-day nosology it seems that Pankejeff suffered from a severe borderline disorder with narcissistic features. His outrageous opening suggestions to Freud, his intense and unresolved narcissistic transference, and his transient psychotic decompensation all tend to support this diagnosis. His grandiose narcissism was sustained in later years by his view of himself as the most famous psychoanalytic case (or as the Wolf-Man remembered Freud's words, "a piece of psychoanalysis" [27]), and he suffered no further psychotic relapses. This has to be viewed as a reasonable outcome given the degree of pathology but one that was a consequence of a therapeutic process very different from that posited by Freud or Brunswick.

DISCUSSION

While it is apparent to the reader of these three case histories that Freud was as much a protagonist in each unfolding clinical drama as the patients themselves, his primary focus remained their intrapsychic context and not their interaction with him. One of the more important developments in psychodynamic theory and technique since Freud's time involves the recognition that a two-person psychology is at work in the clinical situation. As Balint (31) has observed, "our theory and technique refer to events occurring between two people and not simply within one person." The interaction between Freud and his patients, the new object relationship that was formed in the therapeutic setting, is of far greater import than he recognized. For Freud, interpretation was the curative agent, but Loewald (32) has suggested that therapeutic effects are a consequence of ego development resuming in therapy as a result of the relationship with a new object. Loewald drew a parallel between the use of object relations in the formation and development of the psychic apparatus during childhood and the dynamics of the therapeutic process. In his view, the ego development that may take place in therapy is not simply the internalization of objects but an internalization of an interaction process between patient and therapist that includes, but is not confined to, interpretive work. Therapeutic action may thus be viewed as a resumption of growth and the completion of development.

An argument can be made that this process was very much at work in the cases of the Rat Man and the Wolf-Man. Therapeutic effects in Freud's view resulted from the interpretation and working through of instinctual urges, resistances, and transference, whereby what was unconscious became conscious. Cooper (33) has drawn attention to the radical departure from this model represented by Loewald's conception of the interactive role of the therapist, with its emphasis on empathic communication and the therapeutic relationship. He noted that Kohut, shorn of his special metapsychology, is also very close to sharing this outlook. Freud was not unaware of the importance of the therapeutic relationship as a mutative factor in treatment. In one of his last papers (34) he stated that the positive transference "is the strongest motive for the patient's taking a share in the joint work"; however, he did not develop the theoretical implications of the therapeutic relationship and, specifically, of supportive measures in therapy, although, as is clear from the Rat Man and the Wolf-Man cases, he empirically used them.

Similarly, the increasing awareness since Freud's time of the crucial importance of the mother-child relationship in development has led clinicians such as Winnicott (35) to view the psychotherapeutic setting as containing a revival of elements of that relationship. This developmental perspective and its corollary, the importance of preoedipal conflict and dynamics, are generally absent from Freud's case histories, where the emphasis is much more upon the relationship with the father; however, manifestations of preoedipal elements can be seen in his case reports. Mahler's work on self-object differentiation and separation-individuation in the child's preoedipal phase (36) has had a profound influence on modern theories of therapy and practice. Modell (37) has emphasized the relevance of developmental concepts such as the holding environment to the therapeutic situation and the dual function of transference as both a recapitulation of early developmental conflicts and a transference neurosis. These perspectives allow a broader view on the nature of psychodynamic therapy than existed in Freud's time and provide a framework for the psychotherapeutic treatment of the more disturbed patient such as the Wolf-Man.

In his papers on technique (38–42), Freud promulgated clear guidelines and a compelling clinical rationale for preserving therapeutic neutrality. He stated, "As far as his relations with the physician are concerned, the patient must be left with unfulfilled wishes in abundance. It is expedient to deny him precisely those satisfactions which he desires most intensely and expresses most importunately" (42). At first glance, it would appear that Freud abrogated his own maxims in his treatments of the Rat Man and the Wolf-Man. A closer examination of his "extra-analytic" behavior with these two patients, however, draws attention to a complex issue concerning what Stone (43) has called the "real personal relationship" between therapist and patient versus the "true transference reactions." The impact of personal interactions between the therapist and the patient has been a neglected subject in the literature, perhaps because of the uneasy feelings that are stirred up in clinicians who fear that the "purity" of the therapeutic field is compromised by such occurrences. That such personal interactions in the therapeutic encounter are inevitable, however, can hardly be disputed, and Anna Freud has commented,

> But—so far as the patient has a healthy part of his personality, his real relationship to the analyst is never wholly submerged. With due respect for the necessary strictest handling and interpretation of the transference, I still feel that we should leave room somewhere for the realization that analyst and patient are also two real people, of equal adult status, in a real personal relationship to each other. I wonder whether our—at times complete—neglect of this side of the matter is not responsible for some of the hostile reactions which we get from our patients and which we are apt to ascribe to "true transference" only. (44)

Greenson and Wexler (45) have asserted that it is essential to acknowledge, differentiate, and even *nurture* the nontransference or relatively transference-free reactions between patient and therapist in order to facilitate the full flowering and ultimate resolution of the patient's transference. It could be said that Freud did not necessarily breach analytic neutrality in the clinical setting where the transference was involved but that his personal warmth and regard for both the Rat Man and the Wolf-Man, manifest in his extra-analytic actions, fostered the recognition of that "equal adult status" and "real personal relationship" which are intrinsic to the clinical situation and thus enhanced the therapeutic process.

The continuous commentary that the case histories have evoked since their publication speaks to their intellectually provocative quality and the degree to which they can involve the reader. Mahony (46) has asserted that the sometimes fragmentary nature of the clinical material provided by Freud invites the reader to participate and engage in a synthetic process of his or her own. There seems little danger of Freud's case histories becoming mere historical curiosities. Like all truly creative works, they continuously pose new meanings and questions. It can be argued that, as examples of clinical exposition and persuasion, they will never be surpassed. Such a status, however, rather than discouraging the writing of new comprehensive case reports, should foster their appearance. The heuristic value of such comprehensive psychodynamic case reporting is considerable, and the progress of dynamic psychotherapy and the level of scientific discourse concerning its theory and technique would only be enhanced by resurrecting the tradition begun by Freud.

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A Developmental Perspective on Psychotherapy and Psychoanalysis

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Some of the most important issues in dynamic psychiatry involve the mechanisms of action of and the distinctions between psychotherapy and psychoanalysis. Recent advances in developmental psychology and in clinical practice and theory provide new insights into these long-standing controversies.

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Perhaps one of the most important continuing controversies in the widening scope of psychoanalysis involves the distinction between psychoanalysis and psychotherapy. The importance of the controversy derives from the questions raised by the work of Kohut, Gedo, Winnicott, Klein, and others with patients who do not fit comfortably into the psychoneurotic paradigm of psychosexual (oedipal) developmental problems, i.e., patients variously considered to have borderline or narcissistic pathology and dyadic problems. The questions involve the extent to which these patients are being psychoanalyzed (or can be psychoanalyzed) or are being engaged in a more superficial psychotherapeutic process. The purpose of this paper is twofold: to discuss the distinctions between psychotherapy and psychoanalysis from a developmental perspective and to explore some of the mechanisms of action of psychotherapy and psychoanalysis.

The similarities and dissimilarities between psychotherapy and psychoanalysis apparently have been of interest to workers in the field for some time. Strachey's classic article on the therapeutic action of psychoanalysis (1), Eissler's discussion of parameters in psychoanalysis during the early 1950s (2), and the more recent work of Kohut (3–6), Lipton (7), Gill (8), and others attest to both the importance and the thorny nature of the problem of distinguishing between psychoanalysis and psychotherapy. Many of the difficulties in the controversy may involve differing definitions and uses of key concepts and terms, such as psychotherapy, psychoanalysis, transference, transference neurosis, and defense. However, the persistence of the controversy implies that something more than the definition of terms is involved.

Attempts to distinguish between psychotherapy and psychoanalysis have employed many frameworks (9). Some have suggested the notion of a continuum (e.g., supportive psychotherapy—insight-oriented psychotherapy—psychoanalysis) based on various criteria such as intensity, time, and insight orientation. Others have lumped all psychotherapy together and contrasted it to psychoanalysis. Goldberg (9) suggested that in discriminating psychoanalysis from psychotherapy, the difference may lie less in the method than in the goal (the goals being reorganization [psychoanalysis] or repair [psychotherapy] of the self). In the present paper, the goal of analysis is conceived as working through and elucidating the transference, and this goal is conceptually quite distinct from that of psychotherapy even though the latter may use the transference in a variety of ways. Or, as Basch (10) stated, the goal of psychoanalysis is cure through the formation and resolution of the transference, whereas the goal of psychotherapy is the resolution of particular problems.

Much of the confusion about what is psychoanalysis and what is psychotherapy may arise when one focuses on the method involved without using an empirically verifiable developmental model. Use of a developmental perspective means evaluating various terms and interventions used in psychotherapy and psychoanalysis from the standpoint of what such interventions mean at the various stages of a child's development (11–14). The methods used in psychoanalysis and psychotherapy are at times similar, thereby adding to the confusion. The difficulty in distinguishing between psychoanalysis and psychotherapy may occur not so much when one evaluates the goals but rather when one examines the methods employed by each. Various methods or techniques have been labeled psychotherapeutic in the past because they simply led to psychotherapeutic problem resolution and not to the working through of the transference. Currently, however, as I will try to demonstrate, it appears that these same techniques can be shown to lead to analyzable transferences in appro-

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priate situations, e.g., in cases of preoedipal or narcissistic pathology. A developmental perspective is particularly important in attempting to understand how a specific technique can lead to an analyzable transference.

To be more specific, I suggest that difficulties arise in efforts to distinguish psychoanalysis from psychotherapy because the content or type of interventions is evaluated rather than the developmental phase of the patient at the time the interventions are made and the results of such interventions. The understanding of dyadic transferences, based on the early mother-infant relationship, is beginning to catch up with what is known about triadic or triangular oedipal transferences. Interventions that seem to be supportive psychotherapy and may inhibit the unfolding of the transference in a patient with triadic oedipal issues may be precisely what is necessary to facilitate the working through of the transference of a patient with psychopathology on an earlier and/or different level. That is, it is the developmental context of the intervention and not merely the type of intervention itself which determines whether or not the process and ultimate goal are those of psychoanalysis or psychotherapy.

THE LITERATURE

Although a complete literature review of the definitions and history of the distinction between psychoanalysis and psychotherapy is beyond the scope of this paper, I will attempt to address some of the classic papers and positions in order to give the flavor of the controversy. Strachey (1) contended that the mutative interpretation was the critical element in psychoanalysis and that such an interpretation consisted of two phases: one "in which the patient becomes conscious of a particular quantity of id-energy as being directed toward the analyst" and a second in which "the patient becomes aware that this id-energy is directed toward an archaic fantasy object and not toward a real one." Strachey noted that while the mutative interpretation is the ultimate operative factor in the therapeutic action of psychoanalysis, this does not imply the exclusion of many other procedures (such as suggestion, reassurance, and abreaction) as elements in the treatment of any particular patient.

Eissler (2) also focused on interpretation as "basic model technique" in psychoanalysis and introduced the term "parameter of a technique" as "the deviation . . . from the basic model technique . . . , a technique which requires interpretation as the exclusive tool" (p. 110). He suggested that four criteria of a parameter are necessary to fulfill the conditions which are fundamental to psychoanalysis. In essence, these four criteria seem to convey the idea that the parameter must ultimately be analyzed and eliminated.

Alexander (15) explicitly discussed the issue of distinguishing psychotherapy from psychoanalysis, and he addressed the problem from a variety of perspectives. He stated that it was spurious to base the distinction on the external criteria (frequency of sessions, whether or not the patient was on the couch, etc.). Rather, he focused, on the one hand, on the kinds of activity of the therapist and, on the other hand, on the internal psychological processes occurring in the patient. The supportive psychotherapeutic interventions were marked by support of the ego through five procedures: gratifying dependent needs, abreaction, objectively reviewing the patient's situation, aiding the ego's neurotic defenses, and manipulation of the patient's life situation. Uncovering psychotherapy was characterized by use of the transference to uncover and make conscious various factors. Alexander then turned more toward the internal processes in the patient to distinguish between uncovering psychotherapy and psychoanalysis. Psychoanalysis allows for the development of a full-fledged transference neurosis, and this phenomenon represents more than a quantitative difference between psychoanalysis and uncovering psychotherapy. While any uncovering psychotherapy will make use of the transference, only psychoanalysis will systematically penetrate the various and deeper levels of stratification of transference manifestations. This latter process, Alexander suggested, is qualitatively different from what occurs in an uncovering psychotherapy.

In addition to Alexander's work in the early and mid-1950s, a number of articles and panels addressed the topic of the distinction between psychoanalysis and psychotherapy. Panels at two meetings of the American Psychoanalytic Association focused on the issue in 1953, and much of the 1954 volume of the *Journal of the American Psychoanalytic Association* was devoted to it. Discussions of the topic usually involved attempts to define psychoanalysis and psychotherapy and questioned whether there were qualitative differences between the two or whether they were situated on a continuum, with quantitative distinctions separating them (16–19). Perhaps Gill (19) was most specific in his definition of psychoanalysis. He stated, "Psychoanalysis is that technique which, analyzed by a neutral analyst, results in the development of a regressive transference neurosis and the ultimate resolution of this neurosis by techniques of interpretation alone" (p. 775). By emphasizing the role of interpretation, Gill was in agreement with most of the authors I have cited; he differed to some extent by focusing and elaborating on the internal process, i.e., the development of a regressive transference neurosis and the ultimate resolution of this transference.

Thus, the consensus seemed to be that one critical element which separated psychoanalysis from psychotherapy was the former's focus on interpretation, i.e., making unconscious affect and memories available to consciousness. In addition, several authors specified elements more characteristic of psychotherapy that were described as important in supportive therapy and might be preparatory for the interpretive work of psychoanalysis (suggestion, abreaction, manipulation, clarification [18], gratifying dependent needs, abreaction, objectively reviewing the patient's acute stress situation aiding neurotic defenses, and reassurance [1]). As Strachey (1) put it, "A cake cannot be made of nothing but currants" (p. 158). The importance of noninterpretive interventions has also been addressed more recently with the exploration of, for example, extratransference interventions (20) and other nontransference, noninterpretive elements (21). However, the articles in the 1950s as well as some of the more recent work (20, 21) did not use a developmental framework, and thus the critical question remains unanswered if not unaddressed, for one must ask, What does it mean to say that these so-called "supportive psychotherapeutic" interventions are preparatory for interpretive, analytic work?

The work of Gedo and Goldberg (13), Gedo (22), Kohut (6), and Basch (23) more specifically indicated the significance of these noninterpretive interventions by using a developmental framework. Gedo and Goldberg (13) stated, "With every real patient, problems will arise from those areas of psychic life which antedate structural differentiation; these problems cannot be treated by interpretation alone" (p. 160). They described a hierarchy of treatment modalities based on nosology and the developmental level of the patient: pacification for traumatic states (termed "mode I"), unification for psychotic disintegration (mode II), optimal disillusionment for narcissistic personality disorder (mode III), and interpretation for neurotic character disorder (mode IV). Gedo and Goldberg referred to the first three interventions as "the therapeutic action of nonanalytic therapies" and concluded that "successful therapeutic intervention in patients with relatively archaic organization of the psyche is indeed possible. . . . Success in such efforts depends primarily on the use of technical modalities of treatment different from that of psychoanalysis proper, that is, on interventions other than interpretation. . . . The analyses of such patients almost always require the utilization of parameters. . . . We have defined the necessary parameters as pacification, unification, and optimal disillusionment" (pp. 167–168). While Gedo and Goldberg defined more explicitly the psychotherapeutic interventions described by other authors and indicated that these interventions have a particular role according to the patient's developmental phase, they still defined psychoanalysis by a specific type of intervention (interpretation) and a specific type of patient (neurotic character disorder).

Gedo and Goldberg's emphasis on a hierarchy of treatment and the developmental phase of the patient (13) does convey the sense that it is the context of an intervention, not just the content, which determines whether or not a process is psychotherapeutic or psychoanalytic. Lipton (7), in hypothesizing a distinction between Freud's technique and "modern" technique, also stressed the importance of the context rather than just the content in assessing the appropriateness of an intervention. He wrote, "I think that the essence of the difference between modern technique and Freud's is that the definition of technique has been expanded to incorporate aspects of the analyst's relation with the patient which Freud excluded from technique. Accompanying this expansion, there has been a tendency to evaluate technique on the basis of a standard which can be applied immediately to any intervention which the analyst makes without giving consideration to its effect, or lack of effect on the course of the analysis" (p. 262).

More recently, Gedo (22) expanded the concept of psychoanalytic treatment and the type of patient who was analyzable. He stated that when analytic patients "regress to the more archaic modes of mental organization, verbal interpretation—either of the resistances or of the wishes against which they have been erected as defenses—will prove to be insufficient or altogether inappropriate" (p. 18). (The issue of defining "interpretation" is discussed later in this paper.) He then reiterated the three interventions characterizing the three archaic modes within the hierarchy (pacification, unification, and optimal disillusionment). Referring to these interventions and Modell's use of Winnicott's term "holding environment," Gedo stated, "What is under discussion here involves no actual departures from the usual analytic *procedures*: the issue is one of explicitly recognizing certain aspects of the psychoanalytic situation as legitimate and even essential factors in the process of treatment" (22, p. 18; italics in original). "The therapeutic aim of psychoanalysis must be conceptualized as the completion of interrupted developmental processes" (22, p. 20). "In all analyses, therapist-patient 'interactions take place at every level on the developmental hierarchy . . . [owing] to the continuing influence of repressed or disavowed aspects of the personality organized in archaic modes' " (24, p. 225). Thus, Gedo (22, 24) later expanded the definition of psychoanalysis more explicitly than he had in 1973: "According to the more conservative school of thought within psychoanalysis, among these character disorders only those in which oedipal conflicts play a central role in the pathogenesis are analyzable. . . . More radical analysts, notably the followers of Melanie Klein and of other British theorists stressing the importance of object relations, have asserted that disorders based primarily on vicissitudes in the preoedipal phases of development can also be analyzed. . . . Probably the most coherent presentation of the more radical point of view has been that of Kohut" (22, p. 29).

Kohut discussed differences in analytic technique when working with transference neuroses and narcissistic personality disturbances (3), but he adhered to a distinction between psychoanalytic and psychotherapeutic work. A full exposition of Kohut's views on this issue is beyond the scope of this discussion, but two quotes (whose meaning and significance, one hopes, are not too distorted by abbreviation) may serve to illustrate the trends of his thinking. In *The Analysis of the Self* (3), he presented the case of Miss F., which he described as being critical to his understanding of narcissistic personality disorders. In the midst of discussing her treatment, he noted that "although, for tactical reasons (e.g., in order to insure the cooperation of a segment of the patient's ego), the analyst might in such instances transitorily have to provide what one might call a *reluctant compliance with the childhood wish,* the true analytic aim is not indulgence but mastery based on insight, achieved in a setting of (tolerable) analytic abstinence" (p. 291; italics in original). Later, Kohut (6) discussed Schweninger's treatment of Bismarck and stated that "enactments like the one brought about by Schweninger's responsiveness to Bismarck's need for a soothing idealized selfobject lead to psychotherapeutic but not psychoanalytic results unless the transference is interpreted and analytically worked through" (p. 20). A more detailed discussion of the curative factors of psychoanalysis is beyond the scope of this paper, but Kohut's views on understanding and explanation (6), and clinical and theoretical work by Gedo (22, 24) and others (25), should be noted; in addition, Hadley's (26) and Fajardo's (27) efforts to relate neurophysiological and constitutional factors in infancy to clinical concepts of cure are of interest.

Gill (8), in a reexamination of his 1954 paper on psychoanalysis and psychotherapy (19), focused specifically on the analysis of the transference as the essential element of psychoanalysis. "The changes I will propose are more radical than simple extension of the recommendation I made in 1954 that we carry more of the non-directive spirit of psychoanalysis into our psychotherapies" (p. 163). Gill made the recommendation "to broaden the range of the extrinsic criteria [e.g., frequency of sessions and use of the couch] within which the intrinsic criteria can be fulfilled" (p. 163).

Basch (23) used the work of developmental psychology in particular to describe the interpretive process within a developmental framework. He regarded interpretation as essential to analysis and defined interpretation "as explaining or giving the meaning of. . . . We interpret when we believe we have come to understand something about the patient that he or she cannot fathom or organize without our help." Using Stern et al.'s concept of affect attunement (28), Basch suggested that interpretation, or "making the unconscious conscious," includes a variety of interventions, including affect attunement or confirming or validating the patient's affective experiences. These ideas fit with Kohut's discussions of Miss F. in *The Analysis of the Self* with respect to the patient's need for confirmation of her feelings; in Basch's terms this would be affect attunement, and, as Kohut described, this activity was critical to mobilizing the (analyzable) "selfobject" transference.

Historically, then, at least two trends are discernible. First, there has been a trend toward recognizing the analyzability of patients whose primary pathology exists at developmental levels prior to the phase of concrete operations. Second, there has been increased use, or at least increased understanding of such use, of interventions other than transference interpretations in the analysis of patients with pathology at varying levels. To further explore the idea that such interventions can best be termed psychotherapeutic or psychoanalytic only on the basis of context and not content, it is now necessary to explore more fully the issues of interpretation and transference in light of recent advances.

INTERPRETATION

To explore the issue of interpretation, I will take clinical material from Kohut's discussion of his patient Miss F. Miss F. was a 25-year-old woman who sought analysis for a number of diffuse dissatisfactions. Although the process of treatment had the appearance of a well-moving self-analysis, Kohut began to realize that such was not the case. In Kohut's words:

> I came to the crucial recognition that the patient demanded a specific response to her communications, and that she completely rejected any other. Unlike the analysand during periods of genuine self-analysis, Miss F. could not tolerate my silence, nor would she be satisfied with noncommittal remarks; but, at approximately midpoint of the sessions, she would suddenly get violently angry at me for being silent and would reproach me for not giving her any support. I gradually learned, however, that she would become immediately calm and content when I, at these moments, simply summarized or repeated what she had in essence already said (such as, "You are again struggling to free yourself from becoming embroiled in your mother's suspiciousness against men." Or, "You have worked your way through to the understanding that the fantasies about the visiting Englishman are reflections of fantasies about me"). But if I went beyond what the patient herself had already said or discovered, even by a single step only (such as: "The fantasies about the visiting foreigner are reflections of fantasies about me and, in addition, I think that they are a revival of the dangerous stimulation to which you felt exposed by your father's fantasy stories about you"), she would again get violently angry (regardless of the fact that what I had added might be known to her, too), and would furiously accuse me, in a tense, high-pitched voice, of undermining her; that with my remark, I had destroyed everything she had built up; and that I was wrecking the analysis. (3, pp. 285–286)

Kohut then described the nature of his interactions in terms of a narcissistic transference: "During this phase of the analysis the patient attempted, with the aid of my confirming, approving, and echoing presence (mirror transference), to integrate an archaic, narcissistically hypercathected self into the rest of her personality. This process began with a cautious reinstatement of a sense of the reality of her thoughts and feelings" (3, pp. 286–287). In addition, Kohut directly addressed the question of whether the confirmatory nature of his interventions represented merely a "corrective emotional experience":

> At first hearing I might seem to be stating that, in instances of this type, the analyst must indulge a transference

> wish of the analysand; specifically, that the patient had not received the necessary emotional echo or approval from the depressive mother, and that the analyst must now give it to her in order to provide a "corrective emotional experience" [29]. . . . The analytic process in analyzable cases however, as in the case of Miss F., develops in a different way. Specifically I recognized that the patient had reinstated me as the depressive, hypochondriacal mother of her early childhood who had deprived her of the narcissistic nutriment which she had been in need of. Although for tactical reasons (e.g., in order to insure the cooperation of a segment of the patient's ego), the analyst might in such instances transitorily have to provide what one might call a *reluctant compliance with the childhood wish,* the true analytic aim is not indulgence but mastery based on insight, achieved in a setting of (tolerable) analytic abstinence. (3, pp. 290–291)

Upon initial examination, these confirmatory interventions might appear to represent what has historically been called support or reassurance or clarification. Such interventions might be seen primarily as supportive psychotherapy, particularly if taken out of context, i.e., out of the context of the patient's psychopathology and the developing transference. Upon examining these data a second time, however, it appears that such interventions might be viewed as preparatory for future analytic work and interpretation. The interventions might be considered in light of Gedo and Goldberg's hierarchical scheme (13) as unification occurring in mode II (psychotic disintegration) or, in Stern's terms (14), as involving primarily the domain of the emergent self. Indeed, Kohut (3) explicitly addressed the issue of the nature and necessity of these confirmatory interventions within a psychoanalytic framework. In providing the clinical context of Miss F., Kohut suggested that these confirmatory interventions were essential to the mobilization and ultimate analysis of a specific kind of narcissistic transference. Thus, Kohut appeared to conceive of these interventions, when examined in context, not as supportive psychotherapy but as a critical part of the development and resolution of an analyzable transference, i.e., as psychoanalysis. Other clinicians and researchers, from various traditions and schools both before and after Kohut, such as object relations, have similarly described the importance of such interventions in ultimately enhancing analytic work during certain phases of specific patients' treatments (30–32).

It appears, however, that a third examination of these data is not only possible but necessary. For it seems one must ask further, How do these interventions of a confirmatory and organizing nature lead to an analyzable transference, and how does one understand this process from a developmental perspective? Developmental psychology aids in understanding these issues, and it is through such a developmental perspective that the distinction between psychotherapy and psychoanalysis can perhaps be more fruitfully discussed.

The work of Daniel Stern on affect attunement (33) is particularly relevant to understanding developmentally the nature of confirmatory interventions as described by Kohut (3) with Miss F. Defining affect attunement, Stern wrote, "By affect attunement we mean the performance of behaviors that express the quality of feeling of a shared affect state, but without imitating the exact behavioral expression of the inner state. . . . Attunement behaviors are needed to shift the focus of attention to the inside, to the quality of feeling that is being shared. . . . Attunement renders feeling" (pp. 6–7). Stern (14) and Basch (23) have provided examples that convey both the concept of affect attunement and the cross-modal communication which makes the attunement possible. In Stern's example, "a nine-month-old girl becomes very excited about a toy and reaches for it. As she grabs it, she lets out an exuberant 'aaaah!' and looks at her mother. Her mother looks back, scrunches up her shoulders, and performs a terrific shimmy with her upper body, like a go-go dancer. The shimmy lasts only about as long as her daughter's 'aaaah!' but is equally excited, joyful, and intense" (14, p. 140). Basch described Stern's observations as follows:

> An infant was silently reaching for something just beyond his grasp, and at the moment he stretched his mother said "uuuh . . . uuuuh!", participating vocally in the child's muscular effort. In this way the mother conveyed directly to the infant on the sensori-motor level that she shared the experience, that he was understood and that he was not alone. Similarly, when we pick up a baby who is crawling on the floor intending to cradle her in our arms we do not simply swoop down and silently elevate her. We say "Uuuup we go!" Drawing out the vowel so as to mimic the arc in which the child is traveling, ending up as she finishes her journey against our chest encircled by our arms, thereby sharing vocally with her the kinesthetic experience she was having as we picked her up. (23, pp. 34–35)

Stern et al. (14, 28, 33) provided evidence that children have the capacity, especially from 6 months on, to receive and correctly interpret cross-modal messages, e.g., to translate auditory intensity into light intensity, or what is felt into what is seen, and so on. Basch has made the necessary connections between Stern's research in developmental psychology and the clinical situation:

> Through affective attunement the mother is serving as the quintessential selfobject for her baby, sharing the infant's experience, confirming it in its activity, and building a sensori-motor model for what will become its self-concept. Affect attunement leads to a shared world; without affect attunement one's activities are solitary, private and idiosyncratic. . . . If, for whatever reason and on a broader scale, affect attunement is not present or ineffective during those early years, the lack of shared experience may well create a sense of isolation and a belief that one's affective needs generally are somehow unacceptable and shameful. (23, p. 35)

Basch also specifically related the developmental work on affect attunement to analysis and the clinical situation with Miss F.

> Patients with merger needs, like Kohut's Miss F., experience contact as intrusion and want us only to echo their words and moods, the closest they can come to obtaining affect attunement, indicating by their need that tension control through affective communion had failed in significant ways during their development. The long period of affective mirroring that these patients need, as described by Kohut, permits them to overcome the unconscious anticipation of the rejection of their affective needs and the shame that they experience whenever they dare to reach out in that direction; only when that has been accomplished will the patient's resistance to examining his selfobject transference be resolved. (23, pp. 35–36)

Stern (14) also used a developmental framework to elaborate on these clinical processes that are usually termed "mirroring": "I maintain that mirroring is really three different interpersonal processes, each having an age-specific use: appropriate responsivity and regulation (during core relatedness); attunement (during intersubjective relatedness); and reinforcement shaping and consensual validation (during verbal relatedness). Taken together, these are what is usually meant by mirroring" (p. 210).

At this point, one must ask the following question: Are the confirmatory interventions in the context just described "interpretations"? This question highlights the problems involved with the terms applied to the variety of interventions used during the course of an analysis. Gedo and Goldberg (13) confined the term "interpretation" to the treatment modality used in mode IV (psychoneurotic disorders). They thereby distinguished interpretation from the interventions (pacification, unification, optimal disillusionment) used with patients who are dealing with earlier developmental issues. It might be noted that in addition to the effective use of interpretation in psychoneurotic disorders (i.e., mode IV), many clinicians feel that interpretation cannot necessarily be excluded as a meaningful intervention for patients with earlier developmental issues. Stern helped clarify this in discussing as an example the intense aloneness experienced by many so-called borderline patients:

> All domains of relatedness will be involved in the illness, but usually one is experienced as more painful at any time. . . . An empathic approach will inevitably encounter and address the failures in the domain of intersubjective relatedness [i.e., about 7–9 months to 15 months]. . . . An interpretive approach, on the other hand, will inevitably first engage the content material as it exists in the domain of verbal relatedness [i.e., about 15 months on]. . . . The problem is that while all domains of relatedness will be affected, one is likely to be more severely compromised and will require not only more therapeutic attention but perhaps the initial attention that allows treatment to proceed. (14, pp. 265–266)

Gedo (22) addressed the issue of the use of the term "interpretation" explicitly: "It serves conceptual clarity to define an 'interpretation' proper as any therapeutic effort to bring unconscious wishes into awareness" (p. 23). Gedo, of course, emphasized the importance of what he termed "noninterpretive therapeutic interventions . . . in every analysis" (p. 23) but reserved the definition I have just cited for the term "interpretation." Although there may be benefits in restricting the term "interpretation" to that definition, at least two problems are created in doing so, and these must be addressed. First, as Stern et al. (28) and Basch (23) have shown, at early developmental levels confirmatory interventions do make unconscious processes and affects (if not wishes) conscious. Second, there appears to be an unstated equation between interpretation and analysis, yet, as I have indicated, various interventions (such as pacification, unification, optimal disillusionment, or Kohut's confirmatory interventions) are not only appropriate but necessary in the mobilization of analytic transferences.

Turning to the first issue, the work of Stern et al. (28, 33) on affect attunement, as I have described, has been used by Basch to demonstrate that at early developmental levels various affects are made conscious through empathy. In discussing a developmental model of interpretation, Basch (23) stated, "When dealing with problems of affective attunement in the primitive merger, empathy and interpretation were one and the same, or, more accurately, during the preverbal, presymbolic, non-reflective period of sensori-motor development only response in action is registered. When we deal with patients at that stage our echoing of their experience is all that is meaningful" (p. 37). As Kohut (3) described with Miss F., his "confirming, approving, and echoing presence" (p. 286) aided in the beginning of "a cautious reinstatement of a sense of the reality of her thoughts and feelings" (p. 287). Thus, at early developmental levels, various interventions generally accepted to be noninterpretive result in the unconscious becoming conscious.

The second problem with the restrictive definition of interpretation is the implied equation between interpretation and analysis. Indeed, in the analysis of psychoneurotic patients, perhaps this was so. However, as I have described, in the analysis of patients with earlier developmental problems, and even at various phases of the analysis of psychoneurotic patients, interventions other than interpretation are necessary and lead to the mobilization of analyzable transferences. To put it another way, perhaps one should stress that noninterpretive does not mean nonanalytic. If one restricts the term "interpretation" as Gedo (22) did, then the other interventions must be recognized for what they are, namely, analytic interventions, based on a developmental model, that in the proper context lead to an analyzable transference. These other interventions should be viewed within the context of the analysis and not be dismissed as supportive psychotherapy, nonanalytic, etc. The apparent depreciation of such interventions may be due to the lack of understanding heretofore of their significance within a developmental framework.

TRANSFERENCE

It is necessary now to turn to the concept of transference in pursuing the issue of differences between psychoanalysis and psychotherapy. Needless to say, transference has a long clinical and theoretical history, from Freud's many writings on the topic to Strachey's 1934 article (1), Gill's work (8, 19), and the work of many others. Of particular importance to this discussion, however, is the increasing articulation of the sense that many patients somehow seem unable to respond to transference interpretations, either throughout their entire treatment or at certain times during treatment. For example, Kohut (3), in his earlier writings, seemed to be depicting such people when he described patients who treated the therapist as if the therapist were there only to fulfill certain functions rather than dealing with the therapist in an object-related transference. Blum (20) addressed this issue, although from a somewhat different perspective, by focusing on the importance of extratransference interpretations. At least a partial understanding of the problem regarding these patients and transference may be found, as was the case with interpretation, in the realm of developmental psychology, especially in the area of self and object differentiation.

To illustrate some of these issues regarding transference, it may be useful to turn again to clinical material and Kohut's case of Miss F. In addition to the description of the case that I have quoted, Kohut wrote specifically about the nature of the transference of Miss F.

> As I began to realize, the analysand assigned to me a specific role within the framework of the world view of a very young child.... Concomitant with the remobilization of the grandiose self, on which she had remained fixated, there also arose the renewed need for an archaic object (a precursor of psychological structure) that would be nothing more than the embodiment of a psychological function which the patient's psyche could not yet perform for itself: to respond enthusiastically to her narcissistic display and to provide her with narcissistic sustenance through approval, mirroring, and echoing. (3, p. 287)

Kohut described his initial difficulty in understanding this kind of transference:

> Due to the fact that I was at that time not sufficiently alert to the pitfalls of such transference demands, many of my interventions interfered with the work of structure formation.... Thus I refused to entertain the possibility that I was not an object for the patient, not an amalgam with the patient's childhood loves and hatreds, but only, as I reluctantly came to see, an impersonal function, without significance except insofar as it related to the kingdom of her own remobilized narcissistic grandeur and exhibitionism.... For a long time I insisted, therefore, that the patient's reproaches related to specific transference fantasies and wishes on the oedipal level—but I could make no headway in this direction. (3, pp. 287–288)

Basch, in discussing Kohut's description of Miss F., articulated the aspects of the case that make possible the link to developmental psychology:

> The transference of narcissistic patients led to reconstruction of those relationships that antedated self and object differentiation. In these situations, as Kohut established retrospectively, the child seems to need the parent as an extension of his own system, without the parent having an existence of his own—the kind of relationship recaptured in the wish-fulfilling fairy tale of Aladdin.... The analytic evidence indicated that, unlike the neurotic, the narcissistic patient had not gone beyond this stage in his capacity for relationships. On the emotional level the analyst as an individual in his own right did not exist for the patient, while the latter used, or tried to use, the analyst in the transference purely as an impersonal need-fulfilling force. (34, pp. 24–25)

Basch (34) went on to describe Kohut's further work: "Kohut was now able to explore these transferences and found that they could be subdivided into grandiose and idealizing forms.... Together he called these self-object transferences, differentiating them from object-instinctual transferences" (p. 25). It is in the realm of self and object differentiation, then, that these clinical issues regarding early transference manifestations might be better understood; thus, it is necessary to turn briefly to data from developmental psychology. The work of Piaget and Mahler warrants particular attention.

According to Piaget (35, as cited in 36, 37), the child has a concept of "object" when he can conceive of things as substantial, independent of himself, and existing in a context of spatial and causal relations even when they are not present to his perception. The acquisition of this concept proceeds gradually through the last four of the six main stages that Piaget termed the sensorimotor period, i.e., roughly the second year of life. Differences in the timing of the acquisition of this concept involve not only animate versus inanimate objects but also the nature of the attachment of the infant to his mother (36). Basch (38) emphasized the beginning of evocative memory near the end of the sensorimotor period: evocation allows memory independent of immediate perception. In the preoperative period, transformation through imitation adds figurative prethought. As Basch (38) stated, "Figurative prethought, the act of interiorizing experience, and the act of evocative recall . . . separate self as an object from other objects.... Only when the child is capable of objectifying his imaging activity can he become aware of both the activity of imaging and of himself as imager. This ability creates the 'self' and a differentiation of objects that are not self or belong to the 'outside world' " (pp. 236–237).

Mahler and colleagues (39, 40) described self and object differentiation in terms different from those of

Piaget and tended to focus more on the infant's relationship with animate objects, but there are similarities with respect to concepts and timing. Mahler saw the rapprochement subphase (around 15–18 months) as ushering in the child's dawning realization that the mother is actually a separate person and regarded separation and individuation issues as critical as the child approaches 2 years of age. For studies addressing the issue of the earlier differentiation of the infant (self) in behavioral responses to the object, see references 14, 41–43.

For Mahler, the phase of libidinal object constancy begins during the third year and is open-ended. The two principal tasks of this period are the formation of a stable concept of the self and the formation of a stable concept of the other. Libidinal object constancy is not identical to the capacity for object permanence in Piaget's terms (35), and Bell (36) has described these differences in detail. The psychopathology that may result from unsuccessful resolution of the rapprochement crisis, inadequate achievement of libidinal object constancy, or deficiencies related to the latter stages of the sensorimotor period (e.g., evocative memory) has been the subject of much discussion by Mahler (39) and others (44).

Thus, as the work on self and object differentiation suggests, some patients have not reached a developmental level in which the therapist is seen as a separate object. This has profound implications for assessing the nature of transference interpretations. For example, with some patients who lack self and object differentiation, one might not make any transference interpretations for an extended period of time, in order to let a narcissistic transference develop without interference (3). To make a transference interpretation prematurely in this situation not only might interfere with the developing transference but would be out of place, because the patient does not yet have a "self-reflective" capacity. The analyst might focus interpretations on the functions the analyst is providing for the patient but not make object-related transference interpretations based on the therapist as a person, or the interpretations might be focused on so-called extratransference material (20), without specific reference to the analyst as object or function. These various kinds of interpretations, then, are not nonanalytic but, rather, appropriate analytic interpretations, given the developmental level of patients who have not yet achieved self and object differentiation. These interventions are appropriate in that they enhance the development of a transference configuration which can ultimately be articulated and worked through. Although not nonanalytic or unanalytic, such interpretations may be seen as preparatory in the sense that, if all goes well, they can ultimately lead to the formation of an object-related transference neurosis by undoing developmental arrest, allowing self and object differentiation to take place, and permitting the patient to see the analyst as a separate person. However, they are more than preparatory in that structure is formed through both providing and then analyzing the function-fulfilling aspects of the analytic relationship, with the consequent development of self and object differentiation.

CONCLUSIONS

This paper began by examining the question of the distinctions between psychotherapy and psychoanalysis and their mechanisms of action. I hypothesized that the confusion in distinguishing between psychotherapy and psychoanalysis results not so much from their goals (which may be reasonably delineated) but from their methods, particularly when we neglect to use a developmental framework within which to discuss these methods. I suggested that in evaluating whether a process is psychotherapeutic or psychoanalytic, the developmental context within which the intervention is made is primary, and the manner in which it is given is secondary to and dependent on the context. While it may seem self-evident that context as well as content of interpretation must be evaluated (as Gedo and Goldberg [13] have shown), such a stance seems more the exception than the rule in discussions regarding psychotherapy and psychoanalysis. This seems to have come about as understanding of different types of transferences increased (6). Interventions within the earlier types of transferences may have seemed, from their content, to be supportive psychotherapy if they were incorrectly perceived to be occurring within a psychoneurotic framework; however, interventions with the same content can be shown to be psychoanalytic when the context is correctly understood as a narcissistic transference or earlier psychological mode (13).

The developmental approach does not change the basic definition of psychoanalysis as a process focusing on the mobilization and working through of the transference. Rather, what changes is the understanding of transference and interpretation in the clinical setting and the enhancement of that understanding through developmental psychology. With patients developing narcissistic transferences, the transference and developmental level will be seen quite differently than they were in Strachey's (1) or Eissler's (2) time. For instance, to use the example in this paper, interpretation (e.g., confirmatory and validating interventions leading developmentally to a self-system that has the capacity for self-reflection) and transference interventions (e.g., interpreting the relationship in terms of functions rather than separate objects or doing extratransference work) take on very different meanings in the context of a narcissistic transference or a psychoneurotic transference. In dealing with the patient "where one finds him or her," it may be critical, from a developmental perspective, to use the ideas of interpretation and transference that I have described for narcissistic transferences, with the overall psychoanalytic context and goal of allowing a transference to develop and be analyzed. However, if one evaluated some of the interpretations and transference interventions out of context, by content alone, such interventions could be misperceived as supportive psychotherapy due to a misunderstanding of the nature of the transference and the developmental level of the patient.

As Gedo and Goldberg (13) stated, interventions such as pacification and unification may be necessary in any analysis, either because of the momentary regression of a psychoneurotic patient or because the patient's predominant issues are preoedipal. Developmental psychology not only provides further evidence and rationale for this clinical approach but, in addition, allows and forces a different conceptualization of interpretation and transference, which makes possible the psychoanalysis of patients whose pathology has other than a psychosexual focus.

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Psychiatric Syndromes Linked to Reproductive Function in Women: A Review of Current Knowledge

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Four psychiatric syndromes related to reproductive function in women have been identified: postpartum depression, premenstrual syndrome (PMS), post-hysterectomy depression, and involutional melancholia. The authors review what is known about these syndromes and conclude, first, that postpartum depression comprises three separate syndromes, the most severe of which is most likely a variant of primary affective disorder. Second, research into the syndromal nature, biology, and treatment of PMS is still in its infancy due to a variety of methodological difficulties. Third, the rate of depression among women during the involutional period or following hysterectomy for benign pathology is not higher than it is at other times.

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Four psychiatric syndromes that are specifically linked to women's reproductive functions have been described. Three of these syndromes—postpartum depression, premenstrual syndrome (PMS), and post-hysterectomy depression—are, by definition, found only in women. The fourth syndrome, involutional melancholia, has been reported to occur three times more frequently in women than in men (1).

Because our current understanding of these disorders contains a mixture of myths, unwarranted assumptions, conclusions based on old, poorly conducted studies as well as newer, better, data-based research, the purpose of this paper is to clarify and provide up-to-date knowledge.

POSTPARTUM DEPRESSION

It is a deeply held belief that the rate of psychiatric morbidity and depression is higher specifically in the postpartum period. In the past 15 years, data-based studies have increasingly validated this belief. Following uncomplicated childbirth there is a markedly higher rate of psychiatric hospital admissions in women for the first 3 months and a somewhat higher rate for up to 2 years postpartum (2, 3). There are various expressions of this vulnerability, ranging from "the blues" to a florid expression and rapid onset of psychotic depression. However, there is still some doubt about the relationship among these various disorders.

The dispute regarding the phenomenology of postpartum disorders has a long history. Kraepelin and Bleuler believed these were typical syndromes following the stress of pregnancy and birth. *DSM-III-R* does not regard postpartum depression as unique except in its timing and does not give it a separate category.

One can distinguish three separate categories, presented here in the order in which they typically occur following childbirth: postpartum blues, postpartum (puerperal) psychosis, and moderate depression. These are not mutually exclusive subsyndromes, however. Puerperal psychosis, for example, can develop following postpartum blues.

Postpartum blues is, by definition, a common syndrome seen in the first 7 to 10 days postpartum and characterized by emotional lability and tearfulness. Postpartum (puerperal) psychosis is a more uncommon syndrome (1 to 2 per 1,000 births) (2), usually apparent within the first few weeks postpartum and frequently culminating in hospital admission. Moderate depression is a poorly characterized syndrome, possibly indistinguishable from major depressive disorder and described as occurring up to 2 years postpartum.

Postpartum Blues

Most women show some affective lability soon after childbirth; typically, the onset is rapid and symptoms quickly disappear (4, 5). Frequently cited symptoms include crying spells, lability of mood, sadness, subjective confusion, insomnia, and anxiety (4, 6). Although occasionally found to begin on the first postpartum day (4), the peak symptoms generally occur between the third and seventh day (7). In a recent study, however, Levy (8) compared maternity blues to postoperative dysphoria and found striking similarities. The major difference between the two syndromes was in

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the timing of symptoms: postoperative dysphoria ratings were highest right after surgery, but postpartum blues peaked days later. It has been suggested that the delay in symptoms in postpartum blues might be due to the initial euphoria following childbirth that protects the new mother from typical postoperative dysphoria for at least a few days (9).

The peak symptoms of postpartum blues occur during a rapid flux of gonadotropins and hormones. Therefore, many investigators have looked to biochemical variables for an explanation. However, using rating scales sensitive to the kinds of symptoms seen in postpartum blues, Nott et al. (10) could find no correlation between mood ratings and either plasma luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogen, or progesterone, although some associations were found between specific symptoms and hormonal levels.

In a careful series of studies, Handley et al. (11) and Gard et al. (12) found that the absence of the normal increase in total plasma tryptophan seen on days 1 and 2 postpartum was significantly associated with postpartum blues. Unfortunately, tryptophan supplementation was not found to be an effective treatment for postpartum blues in a separate study (13). As Gard et al. (12) suggested, it is more likely that low tryptophan levels reflect some underlying mechanism associated with postpartum blues rather than being etiologically related.

George and Wilson (14) found that platelet monoamine oxidase (MAO) correlated most highly with depression ratings during the first week postpartum. More recently, Ballinger et al. (5), using visual analogue scales, studied women who demonstrated elation in the first week postpartum. These investigators found changes in cyclic plasma AMP during the first week postpartum that differed from those of women who were not elated. Metz et al. (15) found that women with postpartum blues had more platelet γ_2 adrenoreceptor sites than women without postpartum blues.

The correlational nature of these biochemical studies may as likely reflect changes in mood as suggest an etiology for postpartum blues. Also, Handley et al. (11) found that postpartum mood was frequently a continuation of antepartum dysphoria. It would be unlikely that the biochemical changes seen in the first few postpartum days reflect the clinical observations found weeks before. It may also be that women who develop postpartum blues are not biologically different from those who do not but that they simply respond to the normal biological changes with more symptoms, reflecting individual vulnerabilities to common changes.

A few studies that have examined the risk factors for postpartum blues indicate that primiparous pregnancy and history of PMS are the primary predictive variables (4, 10).

At present, postpartum blues can be seen as a normal part of the birth experience. The key therapeutic interventions for postpartum blues are anticipation and reassurance.

Postpartum (Puerperal) Psychosis

A severe, frequently psychotic episode occurs following 1–2 per 1,000 of all births (2, 3). Because these episodes are almost always ascertained in epidemiologic studies by hospital admission, studies of postpartum psychosis allow estimates of severe psychiatric disorders but not of specific syndromal diagnoses (e.g., psychotic depression versus schizophrenia) unless further diagnostic evaluations are made. Additionally, a few severely ill, potentially psychotic patients who are treated as outpatients would be missed in these studies.

Recently, Kendell et al. (3) demonstrated that psychiatric admissions to a hospital were higher by a factor of 6.0 in the first month and by a factor of 3.8 in the first 3 months postpartum compared with antepartum rates. These risk factors are even higher (21.7 and 12.7) if only *ICD-9* psychoses (roughly equivalent to *DSM-III-R* affective disorders and schizophrenia, excluding dysthymia) are included. The higher risk of hospitalization extended up to 2 years postpartum but to a lesser degree. The majority of severe postpartum illnesses began before the third week postpartum. Many of the patients had a history of symptoms during pregnancy. Other episodes were heralded by unusually severe postpartum blues that then progressed into a severe depression.

Most studies have found that approximately 75% to 80% of postpartum hospitalized syndromes are affective in nature; patients with depressive disorders represent approximately 60% of these patients (3, 16–19). Compared with nonpostpartum affective episodes, there is a higher rate of confusion and psychotic symptoms and a higher rate of Schneiderian first-rank symptoms in patients with postpartum affective episodes (16, 17).

Multiple factors exist that are associated with higher risk for severe postpartum disorders. The best documented risk factor is a past history of psychiatric illness (3, 20–22); higher risks are associated with affective disorders specifically, and bipolar disorder probably confers a higher risk than unipolar disorders (3). The best estimate for the risk that a woman with affective disorder will have a puerperal psychosis is 20%–25% (3, 20, 21), a dramatically higher rate than in the population that is not psychiatrically ill.

In general, the risk for affective disorders in the families of women with postpartum episodes is similar to that of women with affective illness that is not postpartum (23). There may be a subgroup of women, however, who have no genetic predisposition to affective disorders and who are at risk for severe affective episodes only in the postpartum period (24). Nonetheless, most of the data on family histories of affective disorder in severe postpartum depressions are consonant with the general notion of postpartum disorders as typical illnesses following a specific stressful event.

Aside from a personal or family history of affective disorder, other risk factors are having a first baby, being unmarried, giving birth by Caesarean section, and perinatal death (2, 3). Social class, obstetric variables (other than Caesarean section), and situational stressors (25) appear to be unimportant.

The risk of future affective episodes following a severe postpartum episode is considerable. Two studies with long follow-ups (5–24 years [18] and 12–16 years [19]) found risks of 34%–38% in postpartum periods and 65% and 51% for nonpostpartum episodes.

Prognosis and treatment are governed primarily by the syndromal nature of the illness. Depressions and manias have good prognoses (17, 18), whereas schizophrenic illnesses have the same generally poor prognosis as does nonpuerperal schizophrenia (18). To our knowledge, no controlled treatment study exists, but the range of prescribed treatment is similar to that of nonpuerperal illness with the possible exception of greater use of ECT in puerperal illness (17).

In summary, the majority of severe postpartum psychiatric disorders may be best viewed as inseparable from nonpuerperal episodes. In our clinical work, we recommend that patients at high risk (those with past psychiatric disorders and, possibly, primiparous women and single women) should be followed closely in the first 2–4 weeks postpartum. The warning signals are early signs of depressive illness, including obsessional thinking, feelings of hopelessness, diurnal variation, and poor sleep (many new mothers tending an infant may report poor sleep patterns, however). Those women who have had multiple affective episodes in the past should consider the prophylactic use of lithium or antidepressants after childbirth; breast-feeding is contraindicated with lithium and discouraged with tricyclics (26). Treatment for an episode in progress should be vigorous to minimize the danger to mother and child and to maximize the mother-infant bonding. Because there is a substantial danger of infanticide (4% in one study [18]), the amount of contact between a psychotic mother and her infant needs to be determined according to the individual aspects of each case.

Moderate Depression

Between the extremes of puerperal psychosis and postpartum blues lies the allegedly higher risk of outpatient mild to moderate depressions in the weeks to months following delivery. The diagnosis of depression has generally been made by using rating scales that measure symptoms, dysfunctions, and visual analogue scales for depression (27, 28). Studies using Research Diagnostic Criteria (RDC) or *DSM-III* criteria for major and/or minor depression have found rates of 8% to 15% (29–31). The milder dysphoric syndromes that do not meet criteria for major depressive episodes would likely be diagnosed as adjustment disorder with depressed mood according *DSM-III-R*.

Virtually all of these studies, however, suffer from the lack of a control group with which to compare rates of disorders. Using more recent epidemiologic data, Cooper et al. (32) found no difference in the risk for nonpsychotic psychiatric disorders over 1 year when comparing a group of postpartum women with a control group of women of the same age, parity, and social class. There was also no difference between postpartum and control women in the types of clinical syndromes seen. If the results of this study are replicated, it would raise the question of whether a specific mild postpartum depression even exists.

In the months following the immediate postpartum period, when women are no longer experiencing enormous biological-hormonal changes, the major life task for new mothers is to deal with the stresses of caring for an infant. Because of this, research has focused on psychological risk factors for postpartum depression. A number of studies have found that undesirable life events and marital problems correlate most highly with depressive symptoms occurring weeks to months after delivery (27, 29, 31, 33). Prepregnancy psychopathology, as indicated by past psychiatric history or high scores on neuroticism scales, has also been associated with a higher risk of depression in some (27, 31, 33) but not all (29) studies. Women with postpartum blues are found to be at higher risk for postpartum depression in most studies (27). Obstetrical difficulties are probably irrelevant in the development of these postpartum depressions (27).

Despite the association between prepartum dysphoric symptoms and postpartum depression, women who are depressed pre- and postpartum seem to represent different clinical groups. Kumar and Robson (29) found that only four of their 22 prepartum depressive subjects were depressed postpartum. Similarly, O'Hara (31) found that only two of 12 prepartum depressed women were depressed 9 weeks postpartum. In general, prepartum depressive syndromes are milder than those seen in the postpartum period. It is unclear how long mild postpartum depressions last. Estimates have ranged from 3.3 weeks (31) to many months (32).

In summary, regardless of whether rates of mild to moderate depression are higher in the first postpartum year, moderate postpartum depressions are probably associated with the acute stress of caring for an infant experienced by a woman who frequently feels alone and unsupported and who may be vulnerable to the effects of these stresses because of either biological vulnerabilities or poor coping skills. Although no controlled treatment study exists, clinical recommendations consonant with this formulation would include psychotherapy with emphases on educating the mother on parenting a young child and supportive approaches, including family therapy to maximize social support. Antidepressants may be helpful if substantial vegetative signs are present.

PMS

Of the four syndromes reviewed in this paper, PMS has received the greatest amount of recent attention. Paradoxically, it is the syndrome least understood. Every imaginable methodological difficulty, including poor syndromal definition, retrospective studies, few controlled treatment trials, and conflicting results in the few methodologically sound studies, have hampered our ability to understand this elusive syndrome.

A syndrome for which no accepted or satisfactory definition is available is difficult to describe. A reasonable definition of PMS is that it is a constellation of mood, behavior, and/or physical symptoms that have a regular cyclical relationship to the luteal phase of the menstrual cycle; are present in most (if not all) cycles; and remit by the end of menstrual flow with a symptom-free interval of at least 1 week per cycle (unpublished data from a workshop on PMS cosponsored by the Center for Studies of Affective Disorders and the Psychobiological Process and Behavioral Medicine Section, Clinical Research Branch, NIMH, April 14–15, 1983). However, aspects of PMS not included in this definition but that must be operationalized include a description of the symptoms, their severity, their time of occurrence, and the baseline of psychological functioning (34).

The role of societal and personal expectations as potential confounding variables is present in nearly all descriptive studies. In Ruble's study (35), a group of undergraduate women were told that they were premenstrual when they were not. This group exhibited significantly higher ratings for water retention, pain, change in eating habits, and sexual arousal compared with another group of women who were told they were 7 to 10 days from menses. Ratings of negative affect, however, showed no such difference. Thus, some but not all symptoms were related to suggestion and expectation.

More than 150 different symptoms have been associated with the menstrual cycle, covering a vast array of physical, psychological, and behavioral symptoms. Most commonly cited among the psychological symptoms are depression, irritability, tension, mood lability, and lethargy. Common physical symptoms are breast tenderness, headache, and edema.

No consensus exists on how best to rate or quantify PMS symptoms. A promising rating scale is the Premenstrual Assessment Form (36), which uses a 6-point scale to cover a variety of physical and psychological premenstrual symptoms and is available in both daily prospective and retrospective versions. The Premenstrual Assessment Form may help to differentiate various types of premenstrual syndromes. The contradictory studies on biological variables may correlate better with specific syndromal subtypes than with PMS in general. At present, most studies do not differentiate between premenstrual syndromes primarily characterized by physical symptoms from those with irritability and depression. Similarly, premenstrual elation and/or hypomania must be distinguished from dysphoria and/or lethargy.

Another methodological problem is the lack of consensus as to severity criteria for PMS. Two common approaches use either a 30% increase in mean negative mood the week before menstruation compared with the week following menstruation (37) or a 2-point increase on a 6-point scale (36). Likewise, no clear definition of "premenstrual" exists. The timing of symptoms can be as diverse as 4 or 14 days before menses, and the duration may extend to the day of menses or 4 days after the onset of menstruation (34).

A major difficulty in interpreting most PMS studies is their use of retrospective data. The best current estimate is that 40%–50% of women who report having PMS do not show symptoms in a predictable relationship to the menstrual cycle when studied prospectively (37–39).

The proposed *DSM-III-R* criteria for PMS, defined as late luteal phase dysphoric disorder, attempt to circumvent many of these methodological difficulties. Late luteal phase dysphoric disorder is classified as a proposed category needing further study. The *DSM-III-R* criteria define the syndrome as a cluster of signs and symptoms (five of ten listed with at least one affective symptom) occurring in the premenstrual week and lasting until a few days after the onset of menses during most menstrual cycles. The criteria also require prospective ratings for a definite diagnosis and impairment in functioning, thereby defining the disorder as it is seen in the small group of consistently symptomatic women rather than the much larger group with milder or less consistent symptoms. The criteria also specifically exclude exacerbations of symptoms of other psychiatric diagnoses as constituting PMS. Unfortunately, it is not clear how this distinction is made, since PMS may be superimposed on another disorder.

Prevalence cannot be accurately assessed in the absence of reliable syndromal criteria. One review (40) concluded that 40% of women experience some mild premenstrual symptoms not associated with change in functioning and that 2%–10% report more severe symptoms with probable functional impairment.

A relatively unexplored methodology that would help separate expectations, symptoms, and biology from psychology would be examination of women who have had hysterectomies but not ovariectomies. Three published studies have examined cyclical symptoms in women who have had hysterectomies. Beumont et al. (41) used daily symptom checklists to study seven women who had hysterectomies and whose cyclical LH and progesterone levels were similar to the normal menstrual pattern. The mean scores of these women for depression and physical and psychological symptoms varied in the same manner over a "cycle" (LH and progesterone were used to time the "premenstrual" phase) as did those of menstruating women; these scores were highest in the "premenstrual" phase. Statistical significance was not reached, but the small number of subjects studied made statistical analysis unreliable. Gath (42) found that 80% of the women who retrospectively reported experiencing PMS before hysterectomy reported similar cyclical symptoms 18 months after hysterectomy. Backstrom et al. (43) also found cyclical changes of mood after hysterectomy in seven women; most symptoms occurred in the late luteal phase.

One review (38) described at least 16 proposed biological etiologies for PMS. As can be expected, all except one of these proposed etiologies were hormonally related. Since Frank's initial paper suggesting excessive estrogen (44) and Israel's suggestion of inadequate luteal progesterone (45) as the prime factors, the most popular theory has been that of an absolute deficiency of progesterone or an abnormally high estrogen-progesterone ratio. A few studies found evidence supporting this theory (46). Unfortunately, there is at least as much evidence suggesting the contrary (47, 48). One recent study (49) could not find any abnormality in the luteal phase in a group of women with PMS compared with a group of women without PMS as documented by endometrial biopsy. In addition, any theory explaining PMS as a syndrome due to a higher estrogen-progesterone ratio must somehow explain the lack of symptoms in the late follicular phase, when estrogen levels are high and progesterone levels are virtually zero. Likewise, the presence of PMS in anovulatory cycles would be theoretically impossible according to this model. Prolactin levels fluctuate throughout the menstrual cycle, with peaks at ovulation and in the late luteal phase. Although suggested as etiologically important in PMS, no consistent abnormalities in prolactin levels have been demonstrated in women with PMS (48).

The role of prostaglandins in PMS has also been questioned, even though the biological role of the various prostaglandins is not yet clear. Hypotheses concerning their role in PMS are equally unclear. Both higher (50) and lower (51) (resulting in abnormal sensitivity to prolactin) levels of prostaglandin have been postulated as being associated with PMS.

Among the many other proposed etiologies for PMS are higher aldosterone levels (causing fluid retention) (52), pyridoxine deficiency (which may cause reduced brain serotonin and dopamine and, secondarily, increased prolactin) (53), and endorphin withdrawal or imbalance (54). The literature on biological etiologies of PMS provides no consistent evidence supporting any one theory. As Clare (55) concluded, "biological research has only served to reveal how complicated the underlying neuroendocrinological framework of the menstrual cycle is. In consequence, theories based on a single hormonal abnormality look increasingly frail."

Psychological theories have in general focused on "neuroticism" (56). Presumably, the physiological symptoms of PMS create an added burden on women who have either poor psychological adjustment and/or show greater sensitivity to normal physiological alterations during the menstrual cycle. This could then manifest itself in more subjective complaints in the premenstrual period. Clare's study (57) casts doubt on this theory. He found that the higher rates of symptoms in psychiatrically disturbed women were psychological and not physical.

Because dysphoric symptoms and inherent cyclicity occur in both, multiple investigations have explored the relationship between PMS and affective illness (56, 58). Although not all studies agree, there seems to be a higher rate of moderate to severe PMS in women with affective illness as well as higher rates of affective illness in women with PMS. Specific methodological conceptual problems include the need to control for treatment variables in examining PMS rates in women with affective disorder and the difficulty in distinguishing between exacerbations of depressive disorders in the premenstrual period from the emergence of PMS as a different symptom complex superimposed on the depression.

Proposed treatments for PMS are largely based on the etiologies mentioned here. Although most uncontrolled trials show positive results, drug versus placebo studies generally find few differences. The usual methodological flaws include subject selection biases and inadequate trial length. There is evidence of a high placebo response rate in PMS (47), thereby decreasing the chance of finding a drug versus placebo difference.

The most popular biological treatment is progesterone supplementation (46). Despite extraordinary positive results in nonblind studies, the double-blind studies using progesterone have shown negative results (59), and controlled trials of oral progestogens have found no difference between drug and placebo (60). Bromocriptine, which lowers prolactin levels, has been studied with inconsistent results in treating mood symptoms, but it is effective in treating mastodynia (61). Of the two double-blind trials using pyridoxine, a low-dose regimen showed no benefit (62) but 500 mg/day was effective (63). Caution in high-dose use of pyridoxine is needed, since it has been reported to cause sensory neuropathy (64). Lithium has been used with poor success in most studies, with the possible exception of a subgroup of patients with cyclothymic disorder, who seemed to respond in one double-blind study (65).

Other hormonal therapies such as oral contraceptives have been used with some success. The most impressive evidence is from a double-blind study by Cullberg (66), who demonstrated that a subgroup of women were made worse by highly estrogenic compounds and better by more progestogenic agents. A controlled study showed more sustained improvement in symptoms from subcutaneous estradiol implant with cyclical norethisterone than with placebo (67). Other treatments studied include gonadotropin-releasing hormone (68) and danazol (69).

Both prostaglandin synthetase inhibitors, such as mefenamic acid (70), and prostaglandin synthesis precursors, such as evening primrose oil (Efamol), which contains γ-linoleic acid (71), have also been prescribed for PMS. Prostaglandin inhibitors are likely to be of benefit in premenstrual and menstrual pain syndromes (72); their efficacy in premenstrual mood syndromes is still unproven. Efamol was effective in one double-blind study (71).

No single therapeutic recommendation for treatment can be made. Because most noncontrolled treatments show extraordinarily good results and high placebo responses are common in double-blind studies, therapeutic optimism is warranted. In addition, there may be subsets of women who respond to one specific agent, as shown by Cullberg (66), even if these women cannot be selected before treatment.

An appropriate treatment plan should first focus on benign "nonspecific" interventions, such as education about PMS, decreasing intake of salt and methylxanthines (e.g., chocolate, cola, and caffeine-containing foods), and exercise (73). This is likely to alleviate the symptoms in a substantial proportion of patients. If more specific medical treatments are needed, treating target symptoms is more likely to be helpful than a more random treatment approach. For instance, the symptoms of swelling and/or edema can be treated with diuretics, but mastodynia is better treated with bromocriptine. Prostaglandin inhibitors such as naproxen or mefenamic acid should be a first choice if dysmenorrhea is the most prominent symptom. Exacerbation of nonmenstrual mood disorders may respond to higher doses of ongoing psychotropic medications. If the major symptoms are those primarily related to negative affect, trials of progesterone suppositories or oral progestins (in the luteal phase), pyridoxine, birth control pills, or prostaglandin precursors can be used. Our clinical experience (and one study [74]) suggests that benzodiazepines used during the luteal phase can be of real value. For each patient, the risks versus the benefits of each of these varied therapies must be evaluated.

POST-HYSTERECTOMY DEPRESSION

Almost 50 years ago, Lindemann (75) suggested that pelvic surgery may be associated with higher rates of postoperative psychiatric morbidity. This gradually evolved to a generally accepted notion that there is a high rate of depression following hysterectomy and to the diagnosis of a separate post-hysterectomy syndrome (76).

Other studies, such as Barker's (77), claimed higher numbers of both new and total psychiatric referrals and psychiatric hospitalizations in the years following hysterectomy compared with the numbers for cholecystectomy patients. The post-hysterectomy syndrome is allegedly characterized by headaches, dizziness, insomnia, tiredness, hot flushes, and urinary symptoms (76, 78). Richards (78) reported that this syndrome and depression are seen more frequently in patients who had hysterectomies than in surgical and nonsurgical control subjects.

There are major methodological problems in these studies, however, including retrospective data collection, unreliably defined psychopathology, and lack of control for preexisting psychopathology. In addition, only some of these studies specifically examined only hysterectomies that were not related to cancer. One would expect different psychiatric sequelae following surgery for cancer compared with surgery for relatively benign conditions.

In contrast to the earlier studies, reports in the last decade are impressive both in their methodology and in the negative results they obtained. These studies indicate that hysterectomy for benign pathology does not lead to more depressive symptoms and may decrease psychiatric symptoms in some women (79–82).

Martin et al. (79, 80) first specifically elucidated preoperative psychopathology as the major determinant of post-hysterectomy psychiatric disturbance. Based on preoperative interviews with 49 women who had hysterectomies for noncancer pathology, the most frequent preoperative diagnosis was hysteria (Briquet's syndrome). In the year following surgery, there were three new psychiatric cases, yielding a 1-year rate of 9%, and no difference in mean self-rated depression scores for the entire group. Six of the seven highest depression scores were in patients who had been diagnosed as having hysteria before the surgery. Of the 11 women with "post-hysterectomy syndrome," 10 had been diagnosed as having hysteria before the surgery. Thus, the presence of depression according to self-rating scale (as opposed to a diagnosis of major depressive episode) and post-hysterectomy syndrome were more frequent in women with a presurgical diagnosis of hysteria. The group as a whole showed no increase in dysphoria, and almost no new psychiatric diagnoses were made.

Gath et al. (81, 82) examined 156 women who had had hysterectomies not related to cancer; follow-up occurred at 6 and 18 months. They found that the number of women diagnosed as having psychiatric disorders according to the Present State Examination decreased by 50% at follow-up and that the reductions were primarily due to fewer women having mild depression or anxiety. Neither age, oophorectomy, surgical factors, nor the absence of objective uterine pathology was associated with postoperative diagnosis of psychiatric disorder. Presurgical psychopathology was the best predictor of postsurgical psychopathology. Noteworthy, however, was the diminution in milder psychopathology for a large number of women in this study. Sixty percent of the women with psychiatric diagnoses before surgery no longer had a diagnosis 18 months after surgery; the majority of these patients had been mildly depressed or anxious.

Based on the best, more recent studies, there is little evidence that hysterectomy is followed by a higher rate of postoperative psychopathology or depression. The subgroup at higher risk is composed of women with preoperative psychopathology. This is consonant with the more general view that the best predictor of the future course for any psychiatric illness may be the past history.

MENOPAUSAL PSYCHIATRIC SYNDROMES

Involutional melancholia (or menopausal depression) seems to be of vanishing interest to psychiatry. For many years it had been believed that there was a specific depressive syndrome occurring in the perimenopausal years. It was usually described as a first-onset agitated psychotic depression with marked features of guilt and somatic preoccupation. Women and men were both diagnosed with this illness, in a ratio of three to one. Despite the proposed existence of male involutional depression, the syndrome was frequently attributed to physiological and psychological effects of menopause. Estrogen supplementation was found to be ineffective.

Articles over the last 25 years, however, show a paucity of evidence for any separate depressive entity occurring in the menopausal years. Two studies that analyzed age-specific risks for affective illness in the perimenopausal period (age range of 45 to 55 years) showed no higher total numbers of depressive episodes, no more new episodes, and no clear difference in symptom patterns in depressive episodes than in other age ranges (83, 84). These findings were confirmed in a Swedish study by Hallstrom and Samuelsson (85).

Milder psychiatric syndromes may occur between age 45 and age 49, although there may be no association between these syndromes and biological menopause. For example, Ballinger's study (86) noted a greater incidence of symptoms in women age 45–49 compared with both older and younger women but found that the higher rate of symptoms were in women who were still menstruating regularly. This finding pointed to the association of psychiatric symptoms with age but not with reproductive status. In addition, physical symptoms of menopause, such as hot flushes and vaginal atrophy, generally do not correlate with psychiatric symptoms (87), whereas psychosocial and psychological variables, such as life events, number of confidants, and relationship with children, may show a stronger correlation (88). Culture-bound expectations may also play a part in menopausal psychopathology, since non-Western cultures may show different or no consistent menopausal symptoms (89).

The only comparatively recent evidence suggesting that major mood symptoms may be linked to the menopausal years comes from studies demonstrating a decrease in some serotonin measures (either plasma free tryptophan [90] or platelet serotonin [91]) in the menopausal and perimenopausal years. This time period correlates with the peak suicide rate for women, a peak not found in men (92). Traskman et al. (93) have suggested that low 5-hydroxyindoleacetic acid (5-HIAA), the final metabolic byproduct of the tryptophan-indoleamine pathway, may be low in suicidal patients, particularly those who commit violent suicides. Although purely speculative at this point, it is possible that the decreased serotonin during menopause temporarily causes a greater susceptibility to suicide in vulnerable women who may also be depressed.

To summarize, more recent research has seemingly put to rest the time-honored concept of involutional melancholia first delineated by Kraepelin. Most experts now accept that "there is no doubt that the involutional psychotic reaction of *DSM-I* has become mythical" (1).

DISCUSSION

Five separate dimensions interact to obscure the research findings in the area of psychiatric syndromes linked to reproductive function in women. These are the psychodynamic aspects of sexuality and reproduction, the substantial hormonal fluctuations associated with reproductive functioning, the problems of imprecise syndrome definition and the variability of the time course of symptoms, culturally biased attitudes toward women, and the failure to identify preexisting psychiatric illness. Each of these issues requires some further discussion.

1. *Psychodynamic aspects of sexuality and reproduction.* Sexuality and reproductive capacity are deeply identified with the sense of self. Although pain or other physical symptoms can be frightening regardless of their physical location, gynecologic symptoms or even normal physical changes (e.g., menstruation) may become a potential focus for psychological vulnerabilities and profoundly affect an individual's self-esteem and personal worth. Gynecologic symptoms or changes may then lead to dysphoric mood or depression. Psychodynamic formulations have interpreted post-hysterectomy symptoms as "a woman's inability to reintegrate herself through the mourning process due to the loss of an organ with which a powerful self-identification is made" (94). Similarly, postpartum depression has been viewed as "a woman unable to accept the full responsibilities of her feminine role, in whom pregnancy and childbirth reactivate early conflicts" (95). Although these formulations may occasionally "fit," they tend to rely on both unproven clinical assumptions and older definitions of depression. Prospective research using reliable measures of self-image and conflicts about sexuality and mothering must be done in order to identify their effect on the expression of the psychiatric syndrome under study.

2. *Hormonal aspects.* Menstrual periods, childbirth, and menopause not only are psychologically meaningful events but also are associated with substantial hormonal fluctuations. The average estrogen and progesterone levels normally drop from 2100 ng/100 ml and 160 ng/ml 2 weeks antepartum to 14 ng/100 ml and 3 ng/ml, respectively, by the fifth postpartum day (10). Such hormonal changes of a hundredfold or more in a matter of days have prompted the observation (with regard to the etiology of postpartum depression) that "the normal adjustment to such sudden alterations in hormone levels . . . is remarkable, rather than an occasional failure" (96). Others have proposed that hormonal imbalances are the primary etiological agents in

premenstrual syndromes. Yet, as reviewed here, studies have been unable to consistently demonstrate biological-hormonal abnormalities in women with postpartum depression or PMS. Just as research on unipolar and bipolar disorder has replaced the "too much or too little" hypothesis with formulations based on abnormal regulatory mechanisms (97), future research on the syndromes reviewed in this paper may also need to focus more on biological vulnerability factors and potentially abnormal responses to normal biological changes.

3. *Syndrome definition and time course variability.* Imprecise syndrome definition and variable definitions of the time course of these disorders have caused considerable disparity in the results of the studies reviewed. The clearest example of this is the lack of consensus in defining the symptoms or time course of PMS. For instance, symptoms in midcycle, presumably coinciding with ovulation, are sometimes considered together with premenstrual symptoms as a single process. Similarly, postpartum blues, found in a majority of women in the first 10 days postpartum, are often viewed as part of the same depressive syndrome that expresses itself in a higher rate of psychiatric admissions up to 2 years postpartum. Although validity cannot be assumed from reliability, the adoption of operational criteria, such as recently proposed for late luteal phase dysphoric disorder in *DSM-III-R,* helps to clarify some basic nosological questions in these disorders.

4. *Culturally biased attitudes toward women.* Observations and implied etiological links may more accurately reflect the psychology of the observer (usually a man) than the psychology of the observed. As quoted by Fluhmann (98, p. 1), Pliny exemplified a culturally accepted but biased myth when he remarked that if a menstruating woman approaches, "new wine will become sour, seeds which are touched by her become sterile, grass withers away." The ancient Hebrews prescribed rituals for a menstruating woman's "uncleanness." The role of observer bias and cultural expectation can obviously obscure naturalistic observations of a condition as variable as PMS. The controversy during the adoption of the *DSM-III-R* definition demonstrates the need to distinguish between symptoms and the labeling of these symptoms as a syndrome, with its many adverse stigmatizing connotations. A recent anthropological review (99) noted that although premenstrual symptoms are seen cross-culturally, it is "recognized, defined and treated as a specific syndrome only in Western, industrial cultures" and that PMS expresses conflicting societal expectations for women in our society.

5. *Preexisting psychopathology.* The failure to identify preexisting psychiatric illnesses has posed difficulties in recognizing, conceptualizing, and treating the disorders reviewed. This is demonstrated most clearly in the different conclusions drawn by the retrospective versus prospective studies of post-hysterectomy psychopathology. Similarly, premenstrual exacerbation of an ongoing psychiatric disorder must be distinguished from a syndrome expressed only in the premenstrual phase for our diagnostic categories to have any validity. Current psychiatric research that defines lifetime diagnoses using reliable criteria has helped greatly and needs to be continued in future research.

CONCLUSIONS

Psychiatric syndromes linked to reproductive function in women require continued interest and investigation. As post-hysterectomy depression and involutional melancholia fade into psychiatric history, we find that hysterectomy does not generally produce psychiatric damage and the involutional period is not associated with greater vulnerability to major depression. Postpartum illnesses seem destined to stay with us as consistent clinical entities, but postpartum psychosis is most likely a variant of primary affective illness and not a separate disorder. The single most important risk factor is a past psychiatric history, especially of affective illness. Research into PMS will expand as our methodologies improve.

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Use of Medication and In Vivo Exposure in Volunteers for Panic Disorder Research

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A survey of 794 subjects volunteering for studies of panic disorder with or without phobic avoidance revealed that fewer than 15% had received imipramine and fewer than 15% had undergone in vivo exposure, although the majority had engaged in some form of counseling and had used benzodiazepines. Subjects with spontaneous panic attacks reported more avoidance than subjects with situational attacks. One-half of the subjects were unemployed. The authors recommend wider use of the available effective treatments for panic disorder and phobic avoidance.

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Panic disorder with phobic avoidance is a common and disabling problem. However, in recent years effective pharmacologic and behavioral treatments have been developed. Such treatments can reduce the frequency and intensity of panic attacks and the extent of avoidance and associated problems. Tricyclic antidepressants, high-potency benzodiazepines, and monoamine oxidase inhibitors (MAOIs) have all been shown to reduce panic attacks and avoidance, at least while the medication is being used (1, 2).

Behavioral treatments to reduce phobic avoidance have also been shown to be effective (3, 4). Furthermore, a number of authors (4–6) have suggested that combined pharmacologic and behavioral treatments may be more effective than either alone. There is evidence, however, that many patients do not receive either pharmacologic or behavioral treatment for panic disorder with avoidance. Breier et al. (7), for instance, found that although 59 of 60 agoraphobic patients had received some prior professional treatment for anxiety, only 20 patients had participated in behaviorally oriented group therapy.

The main purpose of this study was to review the previous treatment of subjects applying to participate in panic disorder research projects. The large sample also permitted us to analyze various other clinical features of panic disorder.

METHOD

From late 1983 to 1986, we sent five-page questionnaires to 1,746 subjects responding to mass media stories and requests for subjects to participate in panic disorder research studies and treatment conducted at Stanford University. Sixty percent (1,051 of 1,746) of the questionnaires were returned. Of these 1,051, some were submitted by the same people on different occasions and others contained only minimal information. After duplicate and incomplete forms were eliminated, 794 (45% of the original sample) remained and were entered into a computer for data analysis.

The first part of the questionnaire requested age, sex, marital status, employment status (and if the subject was working, current occupation), current and past medications, alcohol use, medical conditions,

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panic attack symptoms, frequency of panic attacks, age at onset of panic attacks, and history of hospitalization for emotional problems. The subjects were asked to check off which of various psychotherapy procedures listed they had received. One question asked specifically if they had received training in confronting feared situations. The second part of the questionnaire, the Stanford Agoraphobia Severity Scale (8), asked the subjects to rate how they typically behaved in 10 different situations. Each situation was rated from 0 to 4, where 0="can do without anxiety," 1="can do with mild anxiety," 2="can do with severe anxiety," 3="can do only with extreme terror," and 4="cannot do under any circumstances." The 10 situations were shopping alone in a large department store, such as Macy's; being alone at home for 2 days; driving a car alone 20 miles on a freeway; waiting alone 1 mile away from a house; shopping alone in a large grocery store, such as Safeway; being alone in a crowded place, such as a movie theater or church; crossing a busy street alone; eating a complete meal alone at a restaurant like Denny's; using public transportation (e.g., bus or train) alone; and waiting in a long line at a bank or the Department of Motor Vehicles. The scores ranged from 0 to 40.

Thirty-eight patients were each given the same questionnaire within 1 month of the original submission. The percentages of agreement (number of agreements divided by agreements plus disagreements) for four questions were as follows: "Are you currently working?" 100%; "Have you ever taken any medication for anxiety or depression?" 83%; "Have you ever had a panic attack?" 100%; "Have you ever had a spontaneous panic attack?" 92%. The Spearman coefficients for the test-retest reliability of number of panic symptoms endorsed, number of panic attacks in the past week, and age of onset of panic attacks were r=0.64, r=0.73, and r=0.56, respectively (df=36). Test-retest reliability was also determined for the 10 items on the Stanford Agoraphobia Severity Scale; the Spearman coefficients ranged from r=0.69 to r=0.87 (df=36). The Spearman coefficient for the summed score of all 10 avoidance items was r=0.87, df=36. The percentage of subjects who rated at least three avoidance items 2 or higher on both occasions was 94%. All of these percentages of agreement and Spearman correlations are acceptable except for the age at onset of panic attacks. The ratings on the avoidance items were significantly intercorrelated; all r values exceeded 0.30. A factor analysis identified only one factor with an eigenvalue greater than 1, suggesting that the items measure one domain. In addition to the Stanford Agoraphobia Severity Scale, 50 subjects were also given the Marks-Mathews brief self-rating for phobic avoidance (9) and the phobia scale of the SCL-90 (10). The Stanford scale total score was significantly correlated with the scores on these two scales (r=0.36, df=48, p=0.006 and r=0.46, df=48, p<0.001, respectively).

TABLE 1. Marital and Employment Status of 794 Subjects Volunteering for Panic Disorder Research

	Women (N=580)		Men (N=214)	
Characteristic	N	%	N	%
Marital status				
Never married	119	21	59	28
Married	329	57	113	53
Divorced or separated	119	21	38	17
No response	13	2	5	2
Employment				
Working	182	31	100	47
Not working	227	39	52	24
No response	171	30	62	29

RESULTS

The marital and employment status of the sample can be seen in table 1. Seventy-three percent of the sample was female. The mean±SD age of the women was 40±12.1 years, and the mean age of the men was 39.9±11.4 years. Only two-thirds of the subjects reported employment status, but of those who did, 44% of the women and 66% of the men reported having jobs. There were no significant male-female differences on any of the demographic variables.

The mean±SD age at onset of the illness was 27.0±12.5 years, and the range was 1–80 years. The mean±SD duration of illness was 13.0±12.4 years. There was no significant difference between the women and men in age at onset (27.0±12.5 versus 27.2±12.7 years) or duration of illness (13.0±12.5 versus 12.4±12.3 years). Nearly all of the subjects said they had had panic attacks (see table 2). About 20% of both the men and women reported having been hospitalized for psychiatric problems (see table 2). The most common reason given for hospitalization was depression.

The subjects reported a mean±SD of 9.0±3.3 panic attack symptoms (out of 14); the numbers for women and men were 9.2±3.1 and 8.4±3.7, respectively. The mean±SD number of panic attacks in the previous 7 days was 4.5±8.8; 159 (20%) of the subjects reported having had no panic attacks in the previous week. There was no significant difference between the numbers of panic attacks for women (4.3±7.1) and men (5.1±11.5). Subjects who had had spontaneous panic attacks were significantly more avoidant than patients who had not: the mean±SD ratings on the Stanford Agoraphobia Severity Scale were 14.6±10.0 and 9.6±7.9, respectively (t=5.6, df=401, p<0.001, two-tailed).

The percentages of subjects who reported that they could do the specified tasks only with extreme anxiety or terror or not at all can also be seen in table 2. The most common task evoking severe phobic avoidance among the women was using public transportation, which was followed by driving alone, being in crowded places, and waiting in line. The pattern of avoidance was somewhat different for men; the task causing the most avoidance was being in crowded

TABLE 2. Histories of 794[a] Subjects Volunteering for Panic Disorder Research

Characteristic	Women (N=580)[a] N	Women (N=580)[a] %	Men (N=214)[a] N	Men (N=214)[a] %
History of panic attacks				
Ever had a panic attack	565	97	202	94
Ever had a spontaneous panic attack	466	80	150	70
History of hospitalization for psychiatric problems	116	20	43	20
Previous psychological treatment				
No counseling	160	28	63	29
General counseling	228	39	84	39
Relaxation or hypnosis	79	14	38	18
In vivo exposure	22	4	7	3
Other or combination	65	11	19	9
Tasks associated with severe anxiety or terror or cannot do under any circumstances[a]				
Shopping in department store	138	34	45	30
Being alone	126	31	32	21
Driving alone	202	49	38	26
Walking alone	131	32	39	26
Shopping in grocery store	126	31	39	26
Being in crowded places	191	47	64	43
Crossing the street	91	22	24	16
Eating in public	170	41	33	22
Public transportation	220	56	60	40
Waiting in line	187	45	62	42

[a] Data on tasks associated with severe anxiety or terror were not available for all subjects (women, N=411; men, N=150).

places, followed by waiting in line, and using public transportation. The mean±SD score on the Stanford Agoraphobia Severity Scale was 14.3±10.1 for the women and 11.0±8.8 for the men, a significant difference ($t=3.6$, $df=533$, $p<0.001$, two-tailed).

To compare avoidant subjects with nonavoidant subjects, we defined avoidant subjects as those who rated two or more Stanford scale items as "can do with severe anxiety" or rated one item or more as "can do only with extreme terror" or "cannot do under any circumstances." The analysis was done only with subjects who completed all avoidance items (N=452). According to these criteria, 49% of the subjects (N=221) were avoidant. Only 82 (37%) of the avoidant subjects were employed, compared to 134 (58%) of the nonavoidant subjects ($\chi^2=25.2$, $df=1$, $p<0.001$). Surprisingly, fewer of the avoidant subjects than the nonavoidant subjects (20% versus 33%) were in treatment. There were no differences in medication use between the two groups.

Although the majority of men and women had engaged in some kind of treatment, few reported having used in vivo exposure therapy alone (table 2). Furthermore, only 3% of the avoidant subjects (N=6) had received in vivo exposure therapy. Although the subjects were specifically asked if they had received training in confronting their feared situations, a few might have actually had exposure therapy but classified it as "other or combination of therapies." However, at most, only 15% of the women and 12% of the men would have received some form of in vivo exposure therapy.

Data on current medication use were available for 479 women and 183 men. Among these subjects, 55% of the women (N=262) and 44% of the men (N=81) reported using medications to treat their anxiety. Of those using medications, 77% of the women (N=202) and 73% of the men (N=59) were using benzodiazepines. Of note, only 4% of the women (N=18) and 6% of the men (N=11) were taking imipramine and only four patients were taking MAOIs. In total, only 12% of the subjects (N=82) were taking any kind of tricyclic antidepressant. Data on past medication use were available for 470 women and 179 men. Among these subjects, 62% of the women (N=290) and 54% of the men (N=97) reported having taken medications in the past. Only 3% of the women (N=12) and 4% of the men (N=8) reported having taken imipramine in the past. In total, fewer than 25% of the subjects reported having taken tricyclic antidepressants in the past or present. There were no significant differences in number of panic symptoms, number of panic attacks, or extent of avoidance between the subjects who reported current use of these medications and those who did not.

DISCUSSION

The most striking finding of this study was the apparent underutilization of two effective treatments for panic attacks and phobic avoidance: behavior therapy and imipramine. Both have been shown to be effective independently and in combination (2, 4, 6) in reducing the frequency and intensity of panic attacks and phobic avoidance. Our subjects may have underreported their past use of such treatment, but these results are consistent with those of Breier et al. (7), who also found low rates of effective treatments. MAOIs, also shown to be effective, appear to be rarely used.

It is possible that a random community sample would contain many individuals with present or past histories of panic disorder with or without agoraphobia who had received pharmacotherapy and/or behavior therapy and were no longer symptomatic. The subjects applying for research studies are obviously continuing to have problems. On the other hand, 62% of the women and 61% of the men had received some previous psychological treatment, usually general counseling, and most had received some current or past medication, usually benzodiazepines. More than likely, a random survey of a community sample would also reveal the underutilization of imipramine and in vivo exposure therapy. Our results are similar to those of Aronson et al. (11), who studied 90 subjects who called an anxiety clinic after a television show on anxiety. Relatively few had taken tricyclic antidepressants (36%), and only one had taken an MAOI. Nearly half had undergone individual psychotherapy, so these were subjects who had not been newly identified by the mental health system. Aronson et al. did not report how many had undergone in vivo exposure therapy.

Physicians may be reluctant to prescribe imipramine and other tricyclic antidepressants for a number of reasons. Twenty-five percent or more of the patients who take imipramine experience adverse reactions or intolerable side effects even at subtherapeutic doses (3, pp. 442–444). Other patients develop dose-related side effects, such as constipation and dry mouth. While these side effects can be minimized by starting at very low doses (2), combining a high-potency benzodiazepine with imipramine when treatment is initiated (1, 2), or switching to a tricyclic with fewer anticholinergic side effects, their occurrence might make physicians reluctant to prescribe the medication. Furthermore, physicians may not be knowledgeable about the potential benefits of imipramine or other tricyclic antidepressants. Because we did not have interview data on the patients' doses and length of treatment, we did not analyze the adequacy of treatment. Breier et al. (7) and Evans et al. (12) reported that the subjects with anxiety disorder in their samples had not been given adequate trials. Thus, even when prescribed, such medication may not be given at adequate doses or for long enough.

The infrequent use of in vivo exposure is more puzzling as it is a specific, safe, and effective treatment used singly or in combination with medication (2, 3, 13). The most obvious possible reasons for its underutilization are therapists' preference for less directive psychological approaches and their lack of training in how to use it. Training in exposure therapy should be part of a psychiatric residency curriculum, and a number of available books discuss in detail how to conduct in vivo exposure therapy (2, 3, 13).

Finally, the subjects in this sample were quite disabled. One-half of the subjects were unemployed, 20% had been hospitalized for psychiatric problems, the mean duration of illness was 13 years, and half the women and 40% of the men reported severe or moderately severe anxiety associated with such necessary tasks as shopping and driving.

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Apparent Phase Advance in Diurnal MHPG Rhythm in Depression

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Several investigators have proposed that diurnal rhythms, particularly that of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), show abnormalities in affective disorders. The present study compared diurnal MHPG rhythms in the plasma of 18 male depressed patients and 12 healthy male volunteers. A diurnal rhythm of MHPG closely fit to a cosine model was observed in volunteers and, to a lesser extent, in depressed patients. Patients, especially those with endogenous depression (N=11), demonstrated an earlier acrophase (mean±SD=12.53±3.38 hours), and treatment with desipramine was associated with a significant (3-hour) phase delay. This study confirms and extends previous reports of apparent phase advances in circadian noradrenergic rhythms in depressed patients.

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An increasing number of studies suggest that circadian rhythms of depressed patients differ from those of normal subjects (1–6). One of the most characteristic features of depression is a disturbance of the 24-hour sleep-wakefulness biorhythm (5). Results of sleep EEG studies have demonstrated that the sleep patterns of depressed patients are shifted several hours earlier than normal (1). The case in favor of such phase shifts in depressed individuals is less well established for other circadian measures, with more evidence for either a phase advance or a phase delay for the activity-rest cycle, oral temperature, melatonin, and neurotransmitter receptor density rhythms (7–10) and less appreciable shifts noted for the neuroendocrine measures, such as cortisol (2, 11) and pituitary gonadal hormones (12).

A number of studies support the hypothesis that altered noradrenergic function is central to the pathophysiology of affective illness (13). Clinical studies on the urinary excretion of 3-methoxy-4-hydroxyphenylglycol (MHPG) generally find that there are smaller amounts of this metabolite in the urine of depressed bipolar patients than in normal subjects (14) and, further, that altered excretion rates of MHPG may predict a response to treatment with certain types of antidepressants (15–17). Norepinephrine itself appears to follow a circadian rhythm both centrally and peripherally in animals and in man (18–23). A circadian variation in the norepinephrine metabolites MHPG, vanillylmandelic acid (VMA), and homovanillic acid (HVA) has been found in the urine (3, 6, 24) and plasma (25, 26) of normal volunteers. Sweeney et al. (27) first reported that plasma MHPG rhythms may be altered in depressed patients, and others have conjectured that these differences may be related to a dysfunction of circadian pacemakers (28). Wehr et al. (3) compared the results of a number of studies and suggested that MHPG rhythms in manic-depressive patients may be phase advanced (i.e., have an earlier peak) by approximately 1–3 hours, compared with those in normal control subjects.

An apparent phase advance of circadian plasma MHPG rhythm was first observed by Halaris and DeMet (29) and subsequently reported in urine by Giedke et al. (6) and Pflug et al. (30). A phase-advanced plasma MHPG rhythm has also been reported in attention deficit disorder (31). In a preliminary study we reported that apparent phase advances of the plasma MHPG rhythm in depressed subjects were normalized (phase delayed) after desipramine treatment and that these "corrected" rhythms were more consistent with a simple cosinor model (32). The present study was an effort to confirm and extend our preliminary findings by using a larger sample size, which permitted a more rigorous statistical comparison of our experimental groups.

METHOD

Subjects

Patients were recruited from an inpatient psychiatric unit at a VA medical center. All subjects gave written

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informed consent on a protocol that was approved by the Human Subjects Protection Committee of the UCLA Medical School. Patients met *DSM-III* criteria for major depression or bipolar disorder and Research Diagnostic Criteria (RDC) (33) for primary major depressive disorder, either unipolar or bipolar. On the basis of a structured interview by one of the two principal investigators (H.E.G. and A.E.H.), patients were classified by RDC as having retarded or agitated and endogenous or nonendogenous depression, and unipolar patients were classified as having recurrent or nonrecurrent depression. In addition, we determined the presence of character pathology by RDC and an axis II personality disorder by *DSM-III.*

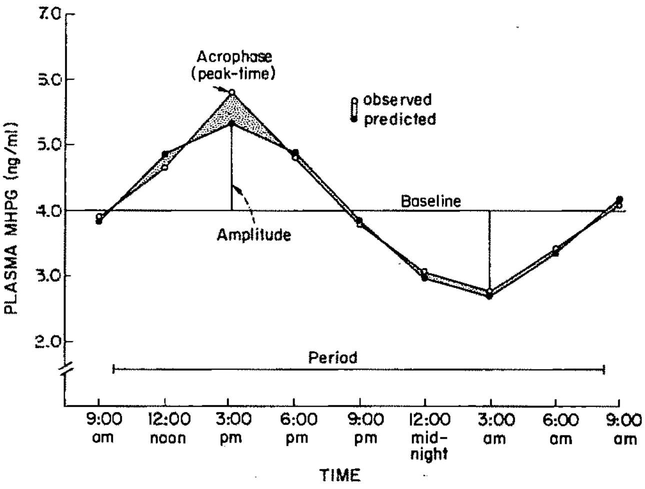
Patients were free of any psychoactive medication for at least 2 weeks before the study. No attempt was made to impose dietary or activity restrictions, since neither has been found to have a significant effect on normal MHPG blood levels (29). The presence of schizophrenia, alcohol, or drug use in either patients or volunteers served as an exclusion criteria. All subjects were required to refrain from the use of any alcoholic beverage for at least 3 days before the experiment (23). Volunteers were recruited by word of mouth and were paid for their participation. All volunteers underwent a physical examination and routine laboratory tests and completed an MMPI and a family history questionnaire. Volunteers were excluded if any abnormalities appeared on any clinical scales of the MMPI (i.e., T score above 70) or if there was major psychiatric pathology in their first-degree relatives. The 18 male patients ranged in age from 29 to 80 years, and the 12 male volunteers ranged in age from 23 to 42 years.

Procedure

Blood samples were collected through an indwelling antecubital catheter, which was kept open by flushing it with sterile citrate-phosphate dextrose buffer. The samples were collected at 3-hour intervals around the clock, and efforts were made to disturb the sleeping patterns of the subjects as little as possible. All subjects slept in an environment that was familiar to them. After the completion of the first diurnal MHPG collection, patients were treated with a daily dose of 150 mg of desipramine for a total of 4 weeks. Changes in clinical status were determined weekly by means of the Hamilton Rating Scale for Depression (34). The diurnal rhythm of MHPG levels in plasma was reexamined after the fourth week of treatment in 10 patients. Total (free plus conjugated) MHPG samples were measured by electron capture gas chromatography (35).

The plasma MHPG values for each subject were best fit to a cosine function that used a nonlinear least squares regression procedure (36). The nonlinear procedure was set to evaluate the residual sum of squares and to arrive at a best set of values for baseline (approximately equal to the mean of all the raw MHPG values), amplitude, acrophase (time of peak MHPG measurement or peaktime), and period length. The residuals of each of these measures were then repeatedly regressed on the partial derivatives of the cosine model by the Gauss-Newton method.

FIGURE 1. Observed and Predicted Mean MHPG Measures in Male Volunteers (N=12)[a]



[a] $r=0.92$, df=11, $p<0.0001$.

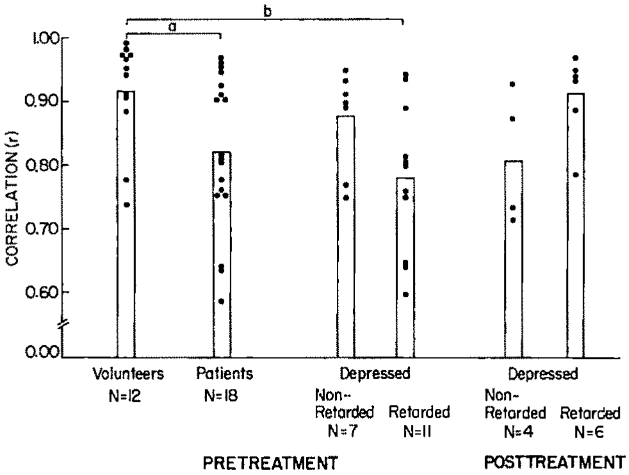
Pearson product-moment correlation coefficients between the observed MHPG values and those values from the predicted model were used as an indication of how well the observed MHPG values fit the model. A lower correlation indicated larger residuals and, therefore, failure to fit into a simple diurnal rhythm. All correlations were subjected to Z transformation before being entered into a parametric analysis of variance (ANOVA). Estimates of values for baseline, amplitude, peaktime, and period were compared in depressed and nondepressed patients and among patients with subtypes of RDC depression by using ANOVA with post hoc Scheffé multiple comparisons or Student's t test. Patients who had at least a 50% decrease in Hamilton depression scores after treatment were classified as responders, and the remainder were considered to have not responded favorably to desipramine. Pretreatment and posttreatment Hamilton scores and estimates of MHPG measures were compared by a repeated measures ANOVA.

RESULTS

Volunteers differed from patients in age (mean±SD=31.4±5.3 versus 47.9±12.4 years; t=5.00, df=25, p=0.0001). The pretreatment (N=18) and posttreatment (N=10) diagnoses of the depressed patients were as follows: endogenous depression, N=11 and N=6; retarded depression, N=11 and N=6; unipolar depression, N=14 and N=7; recurrent unipolar depression, N=6 and N=6; and character pathology, N=11 and N=6.

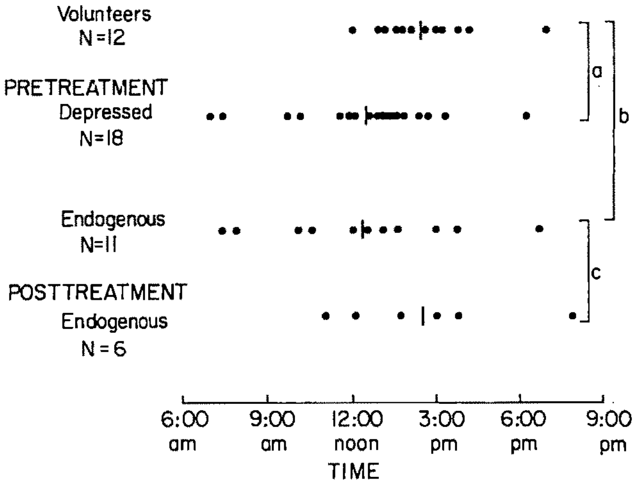
Figure 1 displays diurnal curves for observed and predicted MHPG measures in normal volunteers. The

FIGURE 2. Correlation Between Observed and Predicted MHPG Measures in Male Volunteers and Subgroups of Male Depressed Patients[a]



[a]Bars represent means. Brackets denote significant differences between groups. "a" indicates a lower correlation in depressed patients before treatment (mean±SD=0.82±0.13) than in volunteers (0.92±0.07) (t=2.36, df=28, p=0.03). "b" indicates a lower correlation in patients with retarded depression before treatment (0.78±0.12) than in volunteers and patients with nonretarded depression (0.88±0.08) (p<0.05, Scheffé's test) (F=5.15, df=2, 27, p=0.01).

FIGURE 3. Peaktime (Acrophase) for MHPG Values of Male Volunteers and Male Depressed Patients[a]



[a]Vertical lines represent means. Brackets denote significant differences between groups. "a" indicates that before treatment, depressed patients had a significantly earlier peaktime (13.04±2.72 hours) than volunteers (15.25±1.80 hours) (t=2.46, df=28, p=0.02). "b" indicates an earlier peaktime in patients with endogenous depression (12.53±3.38 hours) than in volunteers (t=2.42, df=21, p=0.02). "c" indicates that the patients with endogenous depression who had both pretreatment and posttreatment data (N=6) demonstrated a significant phase delay to 14.70±3.16 hours after treatment (repeated measures ANOVA: F=5.95, df=1, 5, p<0.05).

correlation between observed and predicted MHPG measures for the depressed patients before treatment was significantly lower than that for volunteers (see figure 2). An examination of RDC subtypes of depression further indicated that patients with retarded depression (N=11) demonstrated significantly lower correlation to the cosine model than patients with nonretarded depression and volunteers (see figure 2). After treatment, neither the patients with retarded depression (mean±SD=0.91±0.07) nor those with nonretarded depression (0.81±0.10) differed significantly from the volunteers (F=2.58, df=2, 19).

Depressed patients demonstrated a significantly earlier peaktime than normal volunteers. This was especially true for the patients with endogenous depression, who had peaktimes approximately three hours earlier than volunteers (see figure 3). Patients with agitated depression did not differ on any measure from patients with nonagitated depression or volunteers. The depressed subjects as a whole did not differ from the normal subjects with respect to baseline MHPG, amplitude, or period length.

Other findings among patients with subtypes of depression in the pretreatment data included the following: The 11 depressed patients with associated character pathology had a lower MHPG baseline than patients without character pathology; normal subjects differed from neither group (F=3.71, df=2, 26, p=0.04). Of the 14 patients with unipolar depression, the six with recurrent depression had a significantly longer period length than patients experiencing their first depressive episode; normal subjects differed from neither group (F=3.46, df=2, 23, p=0.05). After treatment, depressed patients as a whole demonstrated a longer period length than volunteers. This was seen especially in the patients who responded to teatment (F=2.79, df=2, 19, p=0.09) and in the patients with endogenous depression (F=4.92, df=2, 19, p=0.02) (see table 1).

Of the 14 patients who completed the protocol, complete circadian MHPG data were obtained for 10 of them (mean age=45.6±11.4 years). After treatment with desipramine, Hamilton depression scores decreased significantly from 21.0±6.5 to 9.5±7.9 (paired t=3.69, df=9, p=0.005). Seven patients were classified as responders and seven as nonresponders. Of the 10 patients who had complete posttreatment MHPG data, five were desipramine responders. After treatment, the depressed group as a whole did not differ from the normal subjects on the MHPG measures of peaktime, correlation, amplitude, or baseline.

Differences were noted in patients with subtypes of depression after treatment. The mean pretreatment correlation to the cosine model for the six patients with retarded depression who had complete MHPG data was 0.74±0.08; the correlation increased significantly to 0.91±0.07 after desipramine treatment (repeated measures ANOVA: F=20.5, df=1, 5, p=0.006), becoming comparable to the correlation for the volunteers. After treatment with desipramine, the six patients with endogenous depression who had

TABLE 1. Predicted MHPG Measures in Healthy Male Volunteers and Male Depressed Patients

		Baseline (ng/ml)		Amplitude (ng/ml)		Period (hours)		Correlation (Pearson r)		Acrophase (peaktime) (hours)	
Group and Period	N	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Volunteer	12	4.05	1.14	1.46	0.42	21.81	2.88	0.92	0.07	15.25	1.80
Depressed											
Pretreatment	18	4.52	1.78	1.74	0.64	22.49	4.12	0.82	0.13	13.04	2.72
Posttreatment	10	3.76	1.17	1.66	0.70	25.56	7.20	0.87	0.09	13.39	3.23
Retarded											
Pretreatment	11	4.71	1.82	1.88	0.63	23.33	3.08	0.78	0.12	13.13	2.29
Posttreatment	6	3.47	1.00	1.54	0.15	24.93	9.55	0.91	0.07	13.69	3.82
Nonretarded											
Pretreatment	7	4.22	1.83	1.51	0.58	21.17	5.40	0.88	0.08	12.89	3.49
Posttreatment	4	4.19	1.40	1.84	1.16	26.52	1.18	0.81	0.10	12.92	2.52
Endogenous											
Pretreatment	11	4.64	1.89	1.67	0.70	22.32	5.04	0.83	0.10	12.53	3.38
Posttreatment	6	3.96	1.20	1.78	0.88	28.61	7.18	0.86	0.10	14.70	3.16
Nonendogenous											
Pretreatment	7	4.32	1.75	1.84	0.53	22.75	2.43	0.81	0.16	13.83	0.79
Posttreatment	4	3.47	1.22	1.48	0.28	20.98	4.80	0.88	0.10	11.41	2.40
Recurrent unipolar											
Pretreatment	6	4.67	1.71	1.80	0.56	25.12	3.21	0.82	1.27	13.97	3.60
Posttreatment	4	3.53	0.92	1.70	0.20	28.89	9.70	0.88	0.08	15.46	3.24
Nonrecurrent unipolar											
Pretreatment	8	4.97	1.81	1.86	0.76	20.36	4.38	0.83	0.11	12.89	1.87
Posttreatment	3	4.70	0.83	1.96	1.32	24.49	3.03	0.87	0.14	14.01	1.84
Character pathology											
Pretreatment	11	3.93	1.48	1.61	0.53	21.78	3.78	0.84	0.10	13.18	2.82
Posttreatment	6	3.55	1.37	1.66	0.93	14.48	2.52	0.87	0.12	12.63	2.11
No character pathology											
Pretreatment	7	5.78	1.87	2.09	0.71	23.52	5.58	0.81	0.16	12.66	3.23
Posttreatment	4	4.67	0.42	1.72	0.26	21.93	7.56	0.90	0.04	12.59	3.78
Desipramine responder											
Pretreatment	7	4.67	1.61	1.66	0.63	23.38	4.34	0.83	0.13	12.47	3.39
Posttreatment	5	3.59	0.96	1.59	0.25	28.15	8.58	0.90	0.07	14.83	3.26
Desipramine nonresponder											
Pretreatment	7	4.67	2.49	1.66	0.58	22.77	4.55	0.84	0.11	13.19	0.71
Posttreatment	5	3.92	1.43	1.73	1.01	22.97	5.11	0.83	0.11	11.94	2.73

posttreatment data demonstrated a significant phase delay in peaktime from 11.73±3.38 hours to 14.70±3.16, a value also comparable to that of the normal subjects. No such shift was observed among the patients with nonendogenous depression.

In order to determine patterns of association among the estimated MHPG measures in depressed patients and volunteers, correlations were calculated by using all MHPG variables and age. MHPG levels in blood drawn at 9:00 a.m. correlated highly with baseline MHPG in both patients ($r=0.82$, $N=18$, $p=0.004$) and volunteers ($r=0.91$, $N=12$, $p=0.001$). In the depressed patients, period correlated significantly with peaktime ($r=0.78$, $N=18$, $p=0.0001$), and amplitude correlated significantly with baseline ($r=0.70$, $N=18$, $p=0.001$). Age did not correlate significantly with any MHPG variable before treatment, in either patients or volunteers. In the posttreatment phase, age was nonsignificantly correlated with peaktime ($r=-0.55$, $df=9$, $p=0.10$). To control for the effect of age in the comparisons of depressed and nondepressed patients on the peaktime measure, an analysis of covariance was employed.

An analysis was done to compare the variance in MHPG measures between depressed patients and volunteers, and no differences were noted in the variances of any estimated MHPG measure before treatment. However, after treatment, patients demonstrated a larger variance in period length than volunteers (51.81 versus 8.30) ($F=6.24$, $df=9, 11$, $p=0.006$).

DISCUSSION

The major finding of this study is that norepinephrine metabolism, as measured by total plasma MHPG level, appears to have a diurnal variation in both human volunteers and depressed patients. This is in agreement with previous investigations on the circadian rhythm of norepinephrine (18–23), MHPG, VMA, and HVA in volunteers (3, 6, 24, 29, 32, 37) and in depressed patients (3, 30, 32). This finding is also supported by the studies of Kafka (7), which demonstrated circadian rhythms in the densities of alpha_1 and beta adrenergic receptors and in norepinephrine-stimulated cyclic AMP in rats; however, these studies have not been confirmed for the circadian rhythms of alpha_2 adrenergic receptor densities (38). In our normal volunteers, the circadian MHPG rhythm demonstrated an acrophase or peaktime of 15.25±1.80 hours, which is in close agreement with that found by Halbreich and colleagues (reference 39 and U. Halbreich et al. 1986, unpublished data). The finding of an apparent phase advance of this MHPG rhythm is also consistent with the results of some previous investigations (3, 6, 29, 30, 32), although not with all (references 40 and 41 and L.J. Siever et al., 1987, unpublished data). We were able to isolate this abnormality most definitively in the patients with endogenous depression and to demonstrate that treatment with desipramine corrected this phase abnormality. Furthermore, the nonendogenous subgroup did not demonstrate such a phase shift.

What might account for these results? Although the volunteers in this study were younger than the patients, we were not able to relate age consistently to any circadian MHPG variable examined, except for one posttreatment measure. A positive relationship between plasma MHPG and age has been demonstrated in depressed patients (39) and in normal volunteers (42), although other studies have not corroborated this association (43, 44). Other investigators have demonstrated that norepinephrine rhythms could be accounted for by sleep (19, 22), level of perceived stress (20, 21, 45), and alcohol intake (23). Food does not appear to influence the rhythm of epinephrine or norepinephrine (19, 21, 45). Effects of posture and activity upon rhythms of norepinephrine and MHPG are still controversial. Some investigators have found that posture has an effect (19, 21), but the rhythm still appears to exist in volunteers who are confined to bed (22). Similarly, physical activity does not appear to alter the urinary MHPG sulfate excretion level of volunteers (46, 47) or depressed patients (48), although the timing of urinary MHPG excretion appears to parallel daily motor patterns (3). We failed to find any consistent effect of vigorous exercise upon plasma total MHPG levels in both healthy and depressed subjects up to 3 hours after the activity (29).

A recent paper (40) claims to have abolished the rhythm of free MHPG in volunteers and depressed patients by subjecting them to constant conditions of diet, activity, posture, illumination, sleep, and wakefulness. However, in that study the conclusion that "masking" is responsible for the diurnal variation of plasma free MHPG must be evaluated with caution for two reasons: First, the variance around each time point of measurement of plasma free MHPG was high, approaching the variation attributed to the diurnal rhythm. Second, the repeated measures ANOVA used in that study is not as sensitive or reliable a method for exposing diurnal rhythmicity as model curve fitting. Our previous investigations did not point to the need to control for food intake or feeding schedules (29).

In the current investigation, some subjects were awakened briefly at the time of nocturnal blood drawing, and this may have been stressful. In addition, the effects of posture and activity were not controlled in this study. It is possible that these factors may have had some effect on some of the results, although patients were studied and restudied under highly consistent conditions. We recognize that future investigations should attempt to more carefully control for temperature rhythms, posture, level of stress, activity, and sleep measures in order to further elucidate the concomitants of these disordered circadian rhythms of free, sulfoconjugated, and glucoconjugated MHPG.

There has been much controversy concerning the origins of MHPG (49). The present study did not attempt to distinguish between MHPG rhythms of central versus peripheral origin. Whether the central compartment drives or only participates in the circadian variations demonstrated is a question that must be answered by more extensive investigation.

Another finding of this study is that, in general, MHPG rhythms of depressed patients were less synchronized to the circadian cosine model than were those of volunteers. This was especially true for patients with retarded depression. After treatment there was an improvement of this fit, again occurring significantly in patients with retarded depression. MHPG rhythms in patients with nonretarded depression did not demonstrate a correction in the correlation with treatment. Giedke et al. (6), in a study of urinary MHPG, reported similar results in a group of patients with bipolar and unipolar depression. In addition, Giedke et al. did their measurements in a mixed sample of medicated and unmedicated patients. This may have distorted their results, as the effects of the drugs were shown to lengthen period. Pflug et al. (30) demonstrated that the MHPG rhythm was dissociated from the temperature rhythm during the depression stage of a bipolar patient. During her well state, the rhythms were resynchronized.

An important model for the understanding of complex circadian processes has referred to a pair of oscillatory processes. The C (circadian) or deep (x) oscillator is considered the endogenous circadian pacemaker and drives the rhythms of body temperature, cortisol release, urinary potassium excretion, and REM sleep propensity (50). The S (sleep regulating) or labile (y) oscillator is associated with the sleep-wake or rest-activity cycle and with physiological changes linked to changes in posture, timing of meals, and so forth (51, 52). Depressed patients have demonstrated phase advances of the x-rhythm relative to the y-rhythm (53) and lack of synchrony of these two rhythms (54). Experimental manipulations of sleep timing have demonstrated dramatic elevations in mood (55, 56), perhaps by adjusting the degree of synchrony between these two circadian processes. Medication treatment of depression may have a similar effect (54, 57). It is possible that the level of lack of synchrony demonstrated in our population may represent a shifting of one internal *zeitgeber* (process C) from another, or, alternatively, an alteration of the ability of the internal *zeitgeber* to adjust to external cues such as dawn or dusk (10, 58) S process. Demonstration of ultradian periodicity in these MHPG rhythms would be supporting evidence for either of the above hypotheses (59).

The data from the present study were analyzed by nonlinear regression. A recent publication (60) has drawn attention to the limitations of this method, especially when the sampling covers only one full period of the putative circadian rhythm. Consequently, we have reanalyzed the data by using several modifications of the linear least-squares method, with the period fixed at 24 hours. Thus far, the linear modeling techniques have yielded results that largely lend support to the findings obtained from the nonlinear regression analysis.

Like other investigators (5, 30, 59), we did find that after treatment with antidepressant medication, patients demonstrated a longer period length than did volunteers. This was especially true for patients who responded to treatment and in the endogenous subgroup. It is possible that the ameliorative effect of the antidepressant had something to do with increasing circadian period length. As period length increases, phase is delayed. Although we could not demonstrate on repeated measures ANOVA a significant change in our patients with respect to period length, we were able to show that in the depressed patients, period and peaktime (a clock-time expression of acrophase) were highly correlated, whereas in the normal volunteers they were not. It is our hypothesis that period and phase are distinctly related and that this relationship does not appear in volunteers because of the degree of synchronization of their *zeitgebers*.

The finding of a low MHPG baseline in patients with associated character pathology is intriguing and difficult to explain. The low baseline does not appear to be due to agitation or retardation, as patients with these types of depression did not demonstrate a similar degree of abnormality in this measure. Perhaps this result comes about through a type I error, by multiple statistical manipulations. However, before this result is discarded, it is useful to mention that depressed borderline patients appear to demonstrate other biological abnormalities such as abnormal DST results (61–63) and diminished REM latency (64).

One important result of this study is the demonstration that 9:00 a.m. plasma MHPG values were highly intercorrelated with 24-hour mean MHPG levels in both patients and volunteers. If this finding can be replicated, the 9:00 a.m. MHPG sample may be useful as an index of 24-hour MHPG excretion. This might obviate the need for urine collections in estimating MHPG production.

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Interhemispheric Transfer Deficit and Alexithymia

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The hypothesis that alexithymia reflects a functional disconnection between the two cerebral hemispheres was examined in 25 male combat veterans with posttraumatic stress disorder (PTSD). Multiple regression analysis revealed that the efficiency of interhemispheric communication, evaluated with a tactile finger localization task, was a significant predictor of the degree of alexithymia, as measured by the Toronto Alexithymia Scale, independent of PTSD severity and IQ. The PTSD subjects without alexithymia did not differ on the finger localization task from 10 male control subjects without alexithymia. These data suggest that at least some forms of alexithymia may be mediated by an interhemispheric communication deficit.

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Alexithymia, literally meaning "no words for mood," is a term coined by Sifneos (1) to describe a disturbance in affective and cognitive functions. The salient clinical features of alexithymia include difficulty recognizing and verbalizing feelings, a paucity of fantasy life, descriptions of physical symptoms instead of emotions, and speech and thought that are concrete and closely tied to external events (2, 3). The concept of alexithymia evolved from clinical observations by Nemiah and Sifneos (4) and Sifneos (2) of patients with classical psychosomatic disorders. However, alexithymic characteristics are also observed in persons with somatoform disorders (5, 6), substance abuse disorders (7), and posttraumatic stress disorder (PTSD) (7–9) as well as individuals without diagnosable psychiatric disorders (10, 11).

While the etiology and mechanism underlying alexithymia remain unclear, several theoretical models have been described (3, 12). One specific neurophysiological model is based on cerebral hemispheric specialization. The model posits that alexithymia has as a contributory neurophysiological basis a relative lack of communication between the right and left cerebral hemispheres of the brain (13–17). This theory rests on the possibility that emotion is localized in the right hemisphere in most normal right-handed persons (18–20) and that verbal expression is localized in the left hemisphere. The hypothesized lack of communication between the hemispheres in alexithymic individuals would produce a deficit in the ability to verbally articulate emotions.

The theory that alexithymia involves problems in interhemispheric communication evolved from work by Hoppe and Bogen (15), who studied 12 patients before and after cerebral commissurotomy for intractable epilepsy. They observed that after surgery these patients developed a decreased capacity for fantasy, symbolization, and dreams. The similarity in the affective expression and cognitive style of alexithymic and commissurotomy patients led Hoppe (14) to hypothesize that a "functional commissurotomy," or inhibition of corpus callosum activity, may be the basic mechanism underlying alexithymia.

The only direct evaluation of this hypothesis to date was undertaken by TenHouten et al. (21–23), who compared the spoken and written responses of eight patients who had had cerebral commissurotomies (six complete and two partial) and those of eight matched control subjects to questions about a film that symbolically depicted death and loss. The results showed that the patients who had undergone commissurotomy were more alexithymic than the control subjects. Discriminant function analysis (17) found four variables (capacity for symbolization, percentage of affect-laden terms, percentage of auxiliary verbs, and fantasy about symbols) that correctly classified 15 of the 16 subjects. The exception was a control subject who was highly alexithymic, suggesting that complete commissurotomy is a sufficient but not a necessary condition for a high level of alexithymia. An important next step, therefore, would be to determine whether alexithymia in presumably neurologically intact persons may be due to a "functional commissurotomy."

The procedure we selected to assess the functional integrity of the corpus callosum was a tactile finger localization task, a behavioral measure of interhemispheric transfer. The validity of this task as a measure of interhemispheric transfer is founded on anatomical evidence regarding the sensory and motor connections of the hands. Although the somatosensory connections

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from the hands reach both the ipsilateral and contralateral hemispheres, there is evidence that the ipsilateral connections convey only gross information (24). Fine motor control of the fingers is primarily mediated by the contralateral connections rather than the ipsilateral connections (25). Therefore, conditions in which one hand receives a stimulus and the other hand responds (crossed condition) require the interhemispheric transfer of information for successful performance. Evidence that these interhemispheric connections involve the corpus callosum is based on impairment in the ability of commissurotomy patients to cross-localize fingers of the two hands (26–28).

The present study was designed to determine whether alexithymia is associated with a deficit in interhemispheric communication in persons who have not had the corpus callosum surgically transected. Specifically, we predicted that if interhemispheric disconnection is a mechanism underlying alexithymia, then the efficiency of interhemispheric communication should predict the degree of alexithymia in a neurologically intact population.

METHOD

Subjects

The subjects included 25 male Vietnam combat veterans who were consecutively admitted to the Stress Disorder Treatment Unit at the North Chicago Veterans Administration Medical Center and met specific inclusion and exclusion criteria. The unit is a regional referral center for PTSD patients and generally has a waiting list of at least 1 month. Patients who are actively abusing alcohol or other substances must be detoxified if necessary before admission to the unit. Patients are admitted for evaluation and treatment of PTSD symptoms and, typically, a combination of chronic problems including alcohol and/or substance abuse, recurrent difficulty controlling aggression, social isolation, and impaired occupational adjustment.

Patients were clinically evaluated with a modified version of a semistructured interview used in previous research conducted on the Stress Disorder Treatment Unit (29). To be included, patients had to satisfy the *DSM-III-R* criteria for PTSD. Exclusion criteria included evidence of current major depression, psychosis, formal thought disorder, history of coarse brain disease, intracranial mass, epilepsy, cerebrovascular accident, head trauma resulting in significant loss of consciousness, peripheral neuropathy, or any alcohol or substance use within a minimum of 1 week of testing.

Of the 25 patients with PTSD, four patients had no additional diagnoses, 15 had the additional diagnosis of alcohol and/or substance abuse, one had panic disorder, and five had two additional diagnoses: alcohol and/or substance abuse combined with either major depression in remission (two cases) or antisocial personality disorder (three cases). This pattern of comorbidity is very similar to that reported in previous research (29). Three patients were receiving tricyclic antidepressants (daily doses of amitriptyline, 75 mg; desipramine, 200 mg; and imipramine, 150 mg, respectively). The results of these patients were not qualitatively different from those of the 22 unmedicated patients. The patients ranged in age from 36 to 47 years (mean±SD=40±2 years).

Because normative data on the tactile finger localization task for adults are lacking, a control group consisting of 10 individuals was also tested. They ranged in age from 23 to 40 years (mean±SD=34±6 years) and were recruited from faculty and students at the University of Health Sciences/The Chicago Medical School. None of the control subjects had served in combat or had symptoms of PTSD due to other trauma.

Participation in the study was voluntary. All subjects provided written informed consent.

Questionnaires

Edinburgh Handedness Inventory (30). This instrument assesses hand preference. It was used as a gross indicator of cerebral dominance. Only strongly right-handed individuals, defined by a laterality quotient of 70 or higher (31), were selected for this study.

Toronto Alexithymia Scale (32). This scale is a 26-item self-report measure of alexithymia. Scores can range from 26 (no alexithymia) to 130 (highly alexithymic). Although several other scales for assessing alexithymia exist, the Toronto scale appears to be the most psychometrically sound and theoretically relevant self-report measure of the alexithymia construct (32–36).

Several investigators, including the authors of the Toronto Alexithymia Scale, have conceptualized alexithymia as a graded rather than an "all-or-none" phenomenon (3, 7, 35–37) and reported that within a typical alexithymic individual there is considerable variation in the severity and consistency of alexithymic characteristics. For this reason, we analyzed alexithymia as a continuous variable in our main analysis. Taylor et al. (36), however, have established cutoff scores. A Toronto scale score of 62 or less indicates no alexithymia; a score of 74 or more indicates alexithymia. We used these cutoff scores to compose groups with and without alexithymia for secondary analyses. Three of the PTSD subjects scored between 62 and 74 and were, therefore, excluded from the secondary analyses.

Shipley Institute of Living Scale (38). This brief, self-administered scale was used for estimating intelligence. It has a correlation of 0.73 with the WAIS-R full-scale IQ (39).

Posttraumatic Stress Disorder Scale (40). This is a 15-item self-report inventory. Scores can range from 15 (no symptoms) to 60 (many symptoms). Total score on this instrument was used as the measure of PTSD severity.

TABLE 1. Alexithymia, Interhemispheric Transfer, IQ, and PTSD Scores of Normal Control Subjects and PTSD Subjects With and Without Alexithymia

		Score							
		Toronto Alexithymia Scale		Interhemispheric Transfer[a]		IQ		PTSD Scale	
Group	N	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Control subjects	10	54.6	6.6	7.8	4.3	117.8	6.0	—	—
PTSD subjects	25[b]	78.2	16.6	14.9	6.5	103.8	10.2	53.5	5.0
Without alexithymia	7	59.0	2.4	7.6	2.1	102.1	12.4	50.7	6.6
With alexithymia	15	89.3	11.3	18.0	5.6	104.3	10.0	55.9	2.6

[a] Difference score between the mean percentage of correct responses (adjusted for chance performance) for all uncrossed and all crossed localization conditions. Higher numbers equal poorer interhemispheric transfer.

[b] Includes three subjects whose alexithymia scores were between the cutoff scores for PTSD subjects with and without alexithymia.

Procedure

For each subject who met the criteria we have described, interhemispheric transfer was assessed with a tactile finger localization task (26, 41). The subject sat with his hands resting comfortably, palms up, on a table in front of him. The task was demonstrated until it was clear that the subject understood the instructions. The subject was then blindfolded and the following procedure was followed. The examiner lightly touched either one finger or two, three, or four of the subject's fingers sequentially with the sharpened point of a pencil in a predetermined order. After the fingers were stimulated, the subject was requested to indicate which fingers had been touched by touching the fingers with the thumb of the same hand (uncrossed condition) or by touching the corresponding fingers on the other hand with the other thumb (crossed condition). The subject was told which hand was to be stimulated, how many fingers would be touched, and with which hand to respond. No feedback regarding accuracy of response was provided on any trial. A 5-minute rest period was given halfway through the procedure.

Each subject was tested for localization and transfer of one-, two-, three-, and four-finger sequences. There were eight conditions administered in the following order: one-finger localization uncrossed (same hand responding), one-finger localization crossed (opposite hand responding), two-finger localization uncrossed, two-finger localization crossed, etc. There were 40 trials per condition, 20 trials per hand (320 trials total). Half of the subjects were randomly assigned to start with the right hand, and half with the left hand. In each condition each finger was represented an equal number of times; e.g., for one-finger localization uncrossed, each finger was stimulated 10 times per condition, and for two-finger localization uncrossed, 20 times per condition. Another constraint was that within each two-, three-, and four-finger trial, each finger was stimulated only once; i.e., two, three, and four different fingers, respectively, were touched.

For a trial on the tactile fingers localization task to be scored as correct, the subject was required to touch the correct fingers in the same order as stimulated. Percentage of correct responses for each hand was calculated. Since accuracy is differentially influenced by chance performance levels—i.e., chance probability of making a correct response for one-finger stimulation is 25% (one in four), for two-finger stimulation is 8.3% (one in 12), and for three- and four-finger stimulation is 4.2% (one in 24)—the appropriate corrections were applied to the data on correct trials to permit a comparison of performance with different numbers of fingers stimulated. The following formula was used: corrected proportion correct=$[P(C)-C]/(1-C)$, where $P(C)$ is equal to the obtained proportion correct and C is equal to chance probability of a correct response (26). Given that the crossed conditions require interhemispheric transfer and the uncrossed conditions do not, a difference score was calculated between the mean percentage of correct responses (adjusted for chance performance) for all of the uncrossed conditions (right-right and left-left, divided by 2) and all of the crossed conditions (right-left and left-right, divided by 2) (42), which served as an interhemispheric transfer score.

RESULTS

The mean scores on the Toronto Alexithymia Scale, interhemispheric transfer, IQ, and PTSD severity measures for all subjects are shown in table 1. A multiple regression analysis (43) was performed to test whether the efficiency of interhemispheric communication could predict the degree of alexithymia in the PTSD subjects. We used a hierarchical procedure in which Toronto Alexithymia Scale scores served as the dependent variable and PTSD severity, IQ, and interhemispheric transfer scores served as independent variables. PTSD severity scores accounted for 21.58% of the alexithymia variance ($F=6.33$, df=1, 23, $p<0.02$). Subsequent forced entry of IQ accounted for 0.06% more of the alexithymia variance ($F<1$, df=2, 22, n.s.) (results were considered nonsignificant at $p>0.05$ in all analyses). Interhemispheric transfer was entered last and explained an additional 35.58% of the variance, increasing the R^2 to 0.5722 ($F=17.46$, df=3, 21,

$p<0.0005$). These results show a strong association between alexithymia and lack of interhemispheric communication; higher alexithymia scores were associated with a greater deficit in interhemispheric transfer.

A one-way analysis of variance was conducted to test for differences in efficiency of interhemispheric transfer between the control subjects and the PTSD subjects with and without alexithymia. There was a significant main effect of group ($F=19.44$, $df=2, 29$, $p<0.0001$).

Post hoc planned comparisons using the Scheffé test demonstrated that the efficiency of interhemispheric transfer in the control subjects and in the PTSD subjects without alexithymia did not differ significantly, suggesting that PTSD subjects without alexithymia fall in the normal range for adults on this measure. The alexithymic PTSD subjects, however, had a greater deficit in interhemispheric transfer than the normal subjects ($t=-5.36$, $df=22$, $p<0.001$) and the PTSD subjects without alexithymia ($t=-4.89$, $df=19$, $p<0.001$). This suggests that the deficit in interhemispheric transfer is not a function of PTSD but, rather, of alexithymia.

Given that alexithymic individuals have a deficit in interhemispheric transfer, the question arises whether this deficit is specific to interhemispheric transfer or whether these individuals perform poorly on neuropsychological and cognitive tasks in general. To assess one aspect of neuropsychological functioning, we analyzed performance on the uncrossed component of the tactile finger localization task. This measure is sensitive to contralateral cortical damage (44). A comparison of the mean percentage of correct responses made by PTSD subjects without alexithymia (mean±SD=68.4±16.8) and alexithymic PTSD subjects (74.4±15.2) on this measure revealed no significant difference. In addition, we found no significant difference in IQ between the PTSD subjects with and without alexithymia.

Because of the suggested role of the right hemisphere in the mediation of emotion and the role of the left hemisphere in verbal abilities, the possibility exists of either right or left hemisphere dysfunction in alexithymic individuals. To investigate this we compared left-hand with right-hand performance by the alexithymic PTSD subjects in all uncrossed conditions on the tactile finger localization task. No significant difference was found (mean±SD score for the left hand, 75.2±15.7; for the right hand, 73.7±15.8). Furthermore, a comparison of left-hand performance in all uncrossed conditions by the PTSD subjects without alexithymia (67.4±17.8) and that of the alexithymic PTSD subjects did not reveal a significant difference, nor did a comparison of right-hand performance in all uncrossed conditions by the PTSD subjects without alexithymia (69.4±16.4) and that of the alexithymic PTSD subjects. These results suggest that the deficit in alexithymic individuals is not due to a dysfunction in the right or the left hemisphere but, rather, is specific to interhemispheric transfer.

To explore whether alexithymia results from an inability to transfer information specifically from one hemisphere to the other, we compared the measure of transfer of information from the right to the left hemisphere (mean±SD score=17.6±7.6) and the measure of transfer from the left to the right hemisphere (18.5±7.3); no significant difference was found. This suggests that the deficit in interhemispheric transfer in alexithymic individuals is bidirectional.

DISCUSSION

These data support the hypothesis that at least some cases of alexithymia may be mediated by a "functional disconnection" of the two cerebral hemispheres in neurologically intact individuals. After we controlled for PTSD severity and IQ, interhemispheric transfer accounted for 35.58% of the variance in alexithymia. This represents a highly significant relationship.

We demonstrated that the deficit in alexithymic individuals is specific to interhemispheric transfer and is not due to a dysfunction in either hemisphere, as measured by the tactile finger localization task. Additionally, our findings were not due to a general cognitive dysfunction, as measured by IQ. However, we cannot exclude the possibility that an impairment in hemisphere-specific emotional functions exists in alexithymic individuals. Although the finding that PTSD subjects without alexithymia did not differ from control subjects in interhemispheric transfer ability suggests that our results are not attributable to PTSD, we cannot conclude that these findings can be generalized to alexithymic individuals without PTSD. However, current evidence, such as the finding by Krystal et al. (8) that patients with PTSD and patients with psychosomatic disorders displayed comparable degrees of alexithymia, suggests that our findings may be applicable to alexithymic individuals without PTSD as well.

Although caution is warranted because of differing methodologies, the degree of impairment in interhemispheric transfer among alexithymic individuals can be roughly estimated by comparing our results with those of Geffen et al. (26), who studied the effects of corpus callosum lesions on tactile finger localization. On a one-finger tactile localization task, they found a 7% deficit in interhemispheric transfer in normal subjects, a 28% deficit in patients who had had partial commissurotomies (involving lesions of the trunk of the corpus callosum), and an 82% deficit in patients who had had complete commissurotomies. In our sample, over all finger conditions, both the normal subjects and the PTSD subjects without alexithymia showed deficits in interhemispheric transfer of 8%, and the alexithymic PTSD subjects showed a deficit of 18%. These results suggest the comparability of our normal control subjects to those of Geffen et al. (26) and suggest that the deficit in interhemispheric transfer among alexithymic individuals may fall midway between that of normal subjects and partial commissurotomy patients.

One possible reason why the deficit in our patients was not as great as in partial commissurotomy patients is that the tactile finger localization task is not the most appropriate way to assess the deficit in interhemispheric communication associated with alexithymia. To the extent that a greater proportion of callosal fibers carrying emotion-related information relative to the proportion of fibers carrying sensorimotor information from the hands was left intact in the partial commissurotomy patients, a greater deficit would be expected among alexithymic individuals on an interhemispheric transfer task specific to emotional stimuli. This could, perhaps, be tested with lateralized tachistoscopic or dichotic presentation of affect-laden stimuli.

Alternatively, one would not necessarily expect the magnitude of the interhemispheric transfer deficit in alexithymia to be as great as that observed in patients with surgically transected callosal fibers, since a transected corpus callosum does not allow any transfer of information. Our finding of a deficit in the interhemispheric transfer of sensorimotor information suggests the possibility that alexithymic individuals have a generalized deficit in interhemispheric transfer involving other types of information. However, it remains to be seen whether this holds for emotion-related interhemispheric transfer tasks.

The bidirectional deficit in the interhemispheric transfer of sensorimotor information that this study revealed was not unexpected, since sensorimotor processing is not known to be associated with a particular hemisphere. Emotional processing, however, is thought to be lateralized. Therefore, a unidirectional deficit may be found on emotion-specific tasks, and this possibility should receive further investigation.

One of the unresolved issues in research on PTSD is whether alexithymia generally precedes the trauma and creates a predisposition for the disorder (primary alexithymia) or whether both alexithymia and PTSD result from the trauma (secondary alexithymia). Our finding of an association between interhemispheric transfer and alexithymia does not answer this question but, rather, raises additional ones. For example, it is not known whether, in our PTSD subjects, both a deficit in interhemispheric transfer and alexithymia existed before combat, whether a deficit in interhemispheric transfer existed before combat and predisposed an individual to become alexithymic in the face of trauma, or whether combat experience itself induced both a deficit in interhemispheric transfer and alexithymia.

Further investigation of the functional disconnection model of alexithymia appears warranted. In addition to attempting to replicate our results, future studies should include testing the association between alexithymia and other measures of interhemispheric transfer, using a task with affect-laden stimuli, evaluating groups of alexithymic individuals other than those with PTSD, evaluating within-subject covariation in alexithymia and interhemispheric transfer performance, and determining whether any deficits in intrahemispheric function are associated with alexithymia. Furthermore, determining whether interhemispheric transfer is correlated with the degree of myelinization and volume of the corpus callosum, as measured by magnetic resonance imaging, would constitute a first step in determining whether this functional impairment has structural correlates.

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Chronic Medical Conditions in a Sample of the General Population With Anxiety, Affective, and Substance Use Disorders

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The authors studied the prevalence of eight chronic medical conditions in an adult population sample (N=2,554) with and without psychiatric disorders. Adjusted for age and sex, the prevalence of any lifetime chronic medical condition for persons with any lifetime affective, anxiety, or substance use disorder was 61.4%, 57.1%, and 57.7%, respectively. Each of these percentages was significantly higher than that for persons with no lifetime psychiatric disorder (53.4%). Both lifetime affective and anxiety disorders were uniquely associated with a greater prevalence of any lifetime chronic medical condition, but the only psychiatric disorders uniquely associated with current (i.e., active) chronic medical conditions were anxiety disorders, suggesting that the association between anxiety disorders and chronic medical conditions develops more quickly than associations between medical conditions and other psychiatric disorders.

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Persons with concurrent psychiatric disorders and chronic medical conditions are of great public health interest because they are likely to have functional limitations and incur high treatment costs (1–7). Dvoredsky and Cooley (8), for example, found that inpatients with combined medical and psychiatric disorders were more likely than patients with either type of disorder alone to be discharged to a nursing home. In addition, such persons are difficult to diagnose and treat (9–13), in part because of the overlapping symptoms of medical and psychiatric disorders and the interactions that can occur among treatments for the different types of disorder (9, 14).

In this paper, we provide estimates of the prevalence of eight chronic medical conditions in persons with three types of psychiatric disorders (anxiety, affective, and substance use) relative to the prevalence in persons without any psychiatric disorder. The paper is designed to complement an earlier report that provided estimates of the prevalence of psychiatric disorders in persons with and without chronic medical conditions (15). In that study we found 1) that there was a strong overall association between having any psychiatric disorder and having any chronic medical condition and 2) that persons with any recent chronic medical condition had a high prevalence, relative to those without any chronic medical condition, of lifetime substance use disorders and recent affective and anxiety disorders. Such estimates do not fully describe the extent of coexistence of medical and psychiatric conditions in the general population, however. If the prevalences of specific psychiatric disorders and medical conditions are very different, then conclusions about the associations between the two types of health problems will differ depending on how the index populations are defined, i.e., medical conditions in persons with and without psychiatric disorders versus psychiatric disorders in persons with and without medical conditions.

We describe associations between psychiatric disorders and medical conditions for two prevalence intervals, lifetime and recent. The recent prevalence interval is more clinically interesting, because it serves as an indicator of temporal concurrence, i.e., whether the two types of disorders occurred at the same time. The lifetime prevalence interval provides a broad view of whether an association has occurred during any period in the lifetime of the individual. Because there may be fluctuations over time in the presence and/or severity of both psychiatric disorders and chronic medical conditions, during any one period of observation only one or neither of these kinds of disorders may be present, even if they are associated. Second, because lifetime prevalence, by definition, is equal to or greater than recent prevalence, a test of the association between

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lifetime psychiatric disorders and chronic medical conditions has relatively greater statistical power.

In our earlier paper (15), we reviewed the substantial literature on the prevalence of psychiatric disorders in persons with chronic medical conditions. By comparison, there is a relatively small literature on the prevalence of chronic medical conditions in persons with psychiatric disorders (16–25). Several studies have concluded that primary care and mental health specialty sector patients with psychiatric problems or diagnoses have a high prevalence of one or more medical conditions (10, 12, 17–25). For example, Lilliker (17) found a higher than expected prevalence of diabetes among manic-depressive patients receiving care at a mental health center. Rabkin et al. (18) found that among patients receiving outpatient psychiatric care at a teaching hospital, major depression was three times as common among those with hypertension as among those without hypertension. Kessler et al. (25) found a high prevalence of digestive and genitourinary disorders among patients at a general medical clinic who had psychiatric disorders. Koran et al. (11) found that 45% of county mental health patients had an active physical disease, such as hypertension or diabetes.

These earlier studies have one or more design flaws that limit their conclusions. First, most of the studies examined psychiatric or medical patients treated in particular settings, rather than a sample of the general population. Second, methods of identifying psychiatric disorders and chronic medical conditions varied widely across studies. Third, most studies did not include control samples of persons without psychiatric disorders. Fourth, the studies did not examine the association of medical and psychiatric disorders for several different prevalence intervals. Fifth, the studies did not consistently control for demographic factors when estimating the prevalence of medical conditions in persons with psychiatric disorders. As a result of these limitations, it is not possible, on the basis of the existing literature, to formulate specific hypotheses about the prevalence of chronic medical conditions in persons with specific psychiatric disorders.

The present study was designed to overcome some of these flaws. We used data on *DSM-III*-defined psychiatric disorders in a sample of the general population, and we controlled statistically for confounding with sociodemographic characteristics.

METHOD

The National Institute of Mental Health (NIMH) Epidemiologic Catchment Area Program is a multisite general population survey of the epidemiology of psychiatric disorders and use of health services (26, 27). At the Los Angeles site, staged probability samples of household residents from two mental health catchment areas (East Los Angeles and Venice/Culver City) were drawn. Approximately 50% of the respondents were of Hispanic origin (mostly Mexican-American) (28). For each household, one adult was randomly selected to participate in a series of face-to-face interviews. The first wave of interviews was completed in 1982–1983. The response rate was 68% (N=3,132). Respondents were somewhat more likely than the corresponding household population to be young and Hispanic (29). This paper reports data on all Mexican-Americans and non-Hispanic whites in the sample (N=2,554).

Data on psychiatric disorders were obtained with the NIMH Diagnostic Interview Schedule (DIS) (30–32). For lifetime and 6-month prevalence intervals, we determined the presence of any affective disorder (major depression, dysthymia, or mania), any substance use disorder (alcohol or drug abuse or dependence), any anxiety disorder (panic disorder, phobia, or obsessive-compulsive disorder), and any psychiatric disorder assessed in the DIS.

Our measure of chronic medical disease was a 15-item battery that elicits data on whether the respondent has had specific medical conditions ever in his or her lifetime and whether the respondent is currently under medical care for each condition. The medical conditions were 1) chronic lung disease (emphysema, asthma, other chronic lung disease), 2) diabetes mellitus, 3) heart disease, 4) hypertension, 5) arthritis, 6) physical handicap (amputation, paralysis, birth defect, deafness, blindness), 7) cancer, and 8) stroke and other neurologic conditions. We defined having a current medical disease as either currently having the condition or being currently under care for the condition.

The interview also elicited data on age, job status (scored by the Nam-Powers job status scale) (33), sex, marital status, and ethnicity (categorized as Mexican-American or non-Hispanic white).

We used cross-tabulations to examine the lifetime prevalence of any and each of the eight chronic medical conditions in persons with any lifetime psychiatric disorder, any affective disorder, any anxiety disorder, and any substance use disorder relative to the prevalence in those without any lifetime psychiatric disorder. We conducted a parallel analysis for current medical condition and recent psychiatric disorder. Because we were concerned that the self-report measure of chronic medical conditions might overstate the prevalence of these conditions, we conducted a sensitivity analysis using a more conservative definition of a current chronic medical condition (having a condition that was currently under treatment), and there was no change in the major conclusions. Prevalence estimates were sex- and age-adjusted by a direct method (34). We thought that a strict correction for multiple statistical comparisons, as was done in our earlier study (15), was too conservative for this study because of the large number of significant findings and the consistent direction of the associations. Thus, we discuss findings that were significant at the 0.05 level but also note in the tables whether findings were significant at the 0.01, 0.005, and 0.001 levels.

To determine whether there was a relationship between each indicator of psychiatric disorder and any

TABLE 1. Sex- and Age-Adjusted Prevalence of Lifetime Chronic Medical Conditions in 2,552 Adults[a] With and Without Lifetime Psychiatric Disorders

	Prevalence of Lifetime Psychiatric Disorder									
	None (N=1,622)		Any (N=930)		Affective (N=265)		Substance Use (N=553)		Anxiety (N=371)	
Medical Condition	%	SE	%	SE	%	SE	%	SE	%	SE
Any	39.8	1.2	53.4^b	1.7	61.4^b	3.2	57.1^b	2.0	57.7^b	3.1
Chronic lung disease	7.7	0.8	15.1^b	1.2	20.4^b	3.1	17.4^b	2.0	16.6^c	2.9
Diabetes	5.0	0.7	7.4^d	1.0	7.7	1.4	6.5	1.5	9.5^d	1.7
Heart disease	5.8	0.7	10.6^b	1.1	13.5^c	2.3	10.5^d	2.2	12.6^b	1.9
Hypertension	16.0	0.9	21.5^c	1.5	24.4^c	2.8	22.9^c	2.0	25.9^b	2.6
Arthritis	16.5	0.7	23.0^b	1.3	25.1^c	5.1	25.6^b	2.3	25.1^b	1.7
Physical handicap	4.7	0.7	7.3^d	0.9	11.0^d	2.4	10.0^d	2.1	8.0^d	1.5
Neurologic disorder	3.1	0.5	5.3^d	0.8	7.9^d	1.7	4.0	1.0	6.3	1.5
Cancer	2.7	0.4	2.8	0.6	1.7	0.7	3.0	1.1	2.6	0.8

[a] Two persons were excluded because of missing data.

[b] Significantly different ($t>3.30$, $df\geq1885$, $p<0.001$) from percentage for persons with no psychiatric disorder (same row).

[c] Significantly different ($t>2.81$, $df\geq1885$, $p<0.005$) from percentage for persons with no psychiatric disorder (same row).

[d] Significantly different ($t>1.96$, $df\geq1885$, $p<0.05$) from percentage for persons with no psychiatric disorder (same row).

medical condition after the effects of other psychiatric disorders and sociodemographic factors had been controlled, we developed logistic regression models with any lifetime or any current chronic medical conditions as the dependent variables and the demographic variables (age, sex, job status, marital status, and ethnicity), psychiatric disorder indicators, and interactions between ethnicity and psychiatric disorder indicators as the independent variables.

Data were weighted to adjust for differential probabilities of selection of subjects within households and across the two catchment areas. The prevalences (percentages) reported here are weighted, but the sample sizes are the actual sample sizes (referred to as "actual N"). For the cross-tabulations, standard errors and significance levels were corrected for the staged sampling design (i.e., they approximate exact variance estimates) by using Taylor series linearization (34, 35). For the logistic regressions, we estimated correction factors from a linear model (36) and applied these to the chi-square statistics for each logistic regression coefficient. Our conclusions were not affected by the presence or absence of these correction factors.

RESULTS

The sample consisted of 2,554 participants, of whom 51.5% (actual N=1,244) were Mexican-Americans. The percentage of women was 50.4% (actual N=1,332), 55.5% (actual N=1,240) were married, and 63.6% (actual N=1,617) were employed. The unweighted mean±SE age of the subjects was 41.1±17.1 years. For further description of the sample, see our earlier report (15).

As shown in table 1, after adjusting for sex and age, we found that persons with lifetime psychiatric disorders (affective, anxiety, or substance use) had a significantly higher prevalence of lifetime chronic medical conditions than persons with no lifetime psychiatric disorder (t values ranged from 5.39, df=370, to 7.42, df=552, each $p<0.001$). Thus, according to our broadest test, there was a positive association with a chronic medical condition for each type of psychiatric disorder studied. Further, as indicated in table 1, these associations were not limited to only one or two medical conditions. Rather, for persons in each psychiatric disorder grouping, the lifetime prevalences of at least five of the eight chronic medical conditions were significantly greater than the comparable prevalences for persons with no psychiatric disorder.

After controlling for effects of other psychiatric disorders and demographic factors by means of multiple regression techniques, we found that each of the three groups of lifetime psychiatric disorders (affective, substance use, and anxiety) was independently associated with having any lifetime chronic medical condition. The logistic regression coefficients were 0.29, 0.27, and 0.23 for these three groups of disorders, respectively (lowest adjusted $\chi^2=6.99$, df=1, each $p<0.01$).

The regression results also indicate that the association between lifetime affective disorder and lifetime chronic medical condition differed significantly by ethnicity. The logistic regression coefficient for this interaction was 0.21 (adjusted $\chi^2=4.76$, df=1, $p<0.05$). While the prevalence of any chronic medical condition was greater among persons with than among persons without lifetime affective disorder for both ethnic groups, the magnitude of the difference was relatively greater for Mexican-Americans: for non-Hispanic white subjects (actual N=1,310), the sex- and age-adjusted prevalence of any medical condition for those with affective disorders was (mean±SE) 58.2%±3.9%, and for those without an affective disorder, 46.1%±1.5%; for the Mexican-American subjects (actual N=1,244), the prevalence for those with affective disorders was 66.3%±5.5%, and for those without, 40.9%±1.3%.

As shown in table 2, compared to the prevalence for

TABLE 2. Sex- and Age-Adjusted Prevalence of Current Chronic Medical Conditions in 2,552 Adults[a] With and Without Recent Psychiatric Disorders

	Prevalence of Recent Psychiatric Disorder									
	None (N=2,032)		Any (N=520)		Affective (N=188)		Substance Use (N=188)		Anxiety (N=266)	
Medical Condition	%	SE	%	SE	%	SE	%	SE	%	SE
Any	29.5	0.9	38.4[b]	1.8	42.0[b]	3.5	36.5	4.2	46.6[b]	2.4
Chronic lung disease	4.2	0.5	8.4[c]	1.5	12.2[d]	2.8	7.2	1.9	7.7	2.5
Diabetes	3.8	0.4	6.4[e]	1.2	7.4[e]	1.7	1.9	0.9	8.8[e]	2.5
Heart disease	4.2	0.5	9.1[b]	1.2	9.2	2.6	3.4	1.3	16.2[b]	2.9
Hypertension	10.2	0.6	11.8	1.5	11.3	2.6	3.4[b]	1.4	18.2[e]	3.2
Arthritis	14.1	0.6	18.6[c]	1.5	21.5[e]	3.1	14.8	3.7	24.6[b]	3.0
Physical handicap	4.9	0.6	8.7[c]	1.3	11.4[e]	2.8	10.9[b]	1.1	13.1[e]	2.9
Neurologic disorder	1.1	0.2	2.2	0.7	2.4	1.1	0.0	0.0	4.3	2.1
Cancer	1.3	0.3	1.3	0.6	0.6	0.4	1.5	0.9	0.7	0.5

[a] Two persons were excluded because of missing data.
[b] Significantly different (t>3.30, df≥2218, p<0.01) from percentage for persons with no psychiatric disorder (same row).
[c] Significantly different (t>2.57, df≥2218, p<0.01) from percentage for persons with no psychiatric disorder (same row).
[d] Significantly different (t>2.81, df≥2218, p<0.005) from percentage for persons with no psychiatric disorder (same row).
[e] Significantly different (t>1.96, df≥2218, p<0.05) from percentage for persons with no psychiatric disorder (same row).

respondents with no recent psychiatric disorder, the adjusted prevalence of any current chronic medical condition was significantly higher for persons with any recent affective disorder (t=3.46, df=187, p<0.001) or anxiety disorder (t=6.68, df=265, p<0.001) but not substance use disorder. As with the lifetime prevalence intervals, the positive associations for affective and anxiety disorders were with multiple specific chronic medical conditions. Despite the lack of an overall association between recent substance use disorder and any current medical condition, subjects with a recent substance use disorder had a relatively higher adjusted prevalence of physical handicap (t=4.80, df=187, p<0.001) but a relatively lower prevalence of high blood pressure (t=4.47, df=187, p<0.001).

After controlling for other factors through multiple regression analyses, we found that recent anxiety disorder, but not recent affective or substance use disorder, was significantly associated with any current chronic medical disorder. The logistic regression coefficient for anxiety disorder was 0.37 (adjusted χ^2=15.00, df=1, p<0.001). There were no significant interactions between ethnicity and recent psychiatric disorder indicators in predicting the likelihood of a current chronic medical condition.

DISCUSSION

We found that persons with each type of lifetime psychiatric disorder we studied (affective, anxiety, substance use) had a greater prevalence of multiple lifetime chronic medical conditions than persons without a psychiatric disorder, even after we controlled for sociodemographic factors and the presence of other psychiatric disorders. This result indicates that there is some unique relationship between having any chronic medical condition and having each of these types of psychiatric disorder; but this finding alone does not provide information concerning the nature of these relationships, i.e., which is primary or whether or not they occur contemporaneously.

After controlling for other factors, we also found that persons with recent anxiety disorders, but not other psychiatric disorders, had a greater prevalence of any current chronic medical condition. Thus, we reached different conclusions about the relationships between medical conditions and psychiatric disorders for different psychiatric disorder groups and for the two prevalence intervals. We speculate that the difference in conclusions for lifetime and recent prevalence intervals may be due to the fact that it takes time (longer than 6 months) for the associations between either substance use or affective disorders and chronic medical conditions to develop. A group of persons with recent psychiatric disorders or current chronic medical conditions would be expected to include a high proportion of persons with recent onset of those health problems. If the association between the two health problems takes time to develop, the associations between them would be weak or absent for a recent prevalence interval but strong for a lifetime prevalence interval. The pattern of results for anxiety disorders, in contrast, suggests that it may take relatively little time for the relationship between such disorders and chronic medical conditions to develop. For example, anxiety disorder may be an early reaction to onset of a major medical condition, or a primary anxiety disorder could precipitate the onset of a major medical condition.

Our findings concerning the coexistence of recent anxiety disorders and chronic medical conditions are of particular clinical interest. They suggest that persons with anxiety disorders should be carefully evaluated for diabetes, heart disease, arthritis, and physical handicaps—the specific medical conditions that showed a greater prevalence in subjects with anxiety disorders. For some of these conditions, the treatment of the anxiety disorder could exacerbate the medical condition and vice versa. For example, the sedating effects of anxiolytics could exacerbate any limitations in the functioning of persons with arthritis or physical handicaps. In contrast, stress reduction programs, including use of anxiolytics and relaxation techniques, are sometimes recommended for persons with certain heart conditions, especially coronary heart disease. Such techniques would be especially appropriate for a person who also meets criteria for an anxiety disorder.

While we found that persons with affective disorders had a greater prevalence of many specific chronic medical conditions, these associations were weakened after we controlled for concurrent anxiety disorders. This pattern of results suggests that patients with comorbid medical and affective disorders should be carefully screened for concurrent anxiety disorders. Future studies should determine whether the anxiety component is primary, i.e., whether it preceded the affective disorder.

We found that persons with recent substance use disorder did not have a greater prevalence of any current chronic medical condition. This finding may have been partly due to the strong positive association between recent substance use disorder and presence of a physical handicap balanced by the strong negative association between recent substance use disorder and high blood pressure. The former association could reflect either a tendency of those with new limitations to develop substance abuse as a way of coping or the tendency of substance abusers to injure themselves. The latter association is somewhat surprising, given the evidence that alcohol, the most commonly abused substance, is a major risk factor for hypertension (37). One possible explanation for this finding is that persons with hypertension may have been advised to stop drinking. Alternatively, persons with high blood pressure who are substance abusers may tend to die young and thus be rare in a sample of the general population.

The strength of the relationships between specific psychiatric disorders and specific chronic medical conditions varied somewhat for the two prevalence intervals we studied. For example, persons with lifetime anxiety had a more than twofold higher adjusted prevalence of lifetime chronic lung disease, but the comparable relationship for the recent prevalence interval was weaker and not significant. A similar pattern of results was observed for affective disorder and high blood pressure. The less strong relationships for the recent prevalence interval, as we have noted, may be due to the shorter time required for these specific relationships to develop. We observed the reverse pattern, however, for diabetes and affective disorder: the relationship was stronger for the recent prevalence interval. One possible explanation is that a group of persons with current diabetes might include a relatively high proportion of people with more severe disease, particularly early-onset or insulin-dependent diabetes, while a group with lifetime diabetes might include many persons with mild diabetes. We would expect more secondary depressions among those with more severe diabetes.

Because the Los Angeles project of the Epidemiologic Catchment Area Program included a large subsample of Mexican-Americans, we were able to test the generalizability of our conclusions to both Mexican-Americans and non-Hispanic whites. We found that the relationships between psychiatric disorders and chronic medical conditions were generally similar for the two ethnic groups. There was a stronger relationship, however, between lifetime affective disorders and lifetime chronic medical conditions for Mexican-Americans than for non-Hispanic whites. The finding should be considered tentative or suggestive rather than definitive, however, because this was the only significant difference (out of nine tested) by ethnicity in the relationship between psychiatric disorders and chronic medical conditions. Thus, other studies should attempt to replicate this finding.

A limitation of our study was the reliance on a self-report measure of specific chronic medical conditions. This method may have lead to overreporting of some medical conditions. However, we reached similar conclusions about the relationship between psychiatric disorders and chronic medical conditions when we used a more conservative indicator of current chronic medical conditions (being currently under treatment for a medical condition). This increases our confidence that our main conclusions were not seriously affected by the self-report method. The National Health Interview Survey (38) uses a similar method to assess the presence of specific chronic medical conditions. Although the age groups studied and the methods used differ across studies, our estimates (15) for the adult household sample of Mexican-Americans and non-Hispanic whites in Los Angeles were similar to the National Health Interview Survey national estimates. For example, the prevalence of hypertension was 10.4% in the Epidemiologic Catchment Area study and 12.4% in the National Health Interview Survey, and the prevalence of arthritis was 14.8% and 13.3%, respectively. In addition, evidence is accumulating that self-reported chronic medical conditions are strongly related to use of services and level of day-to-day functioning (39–41). Thus, even if our method overstates the prevalence of chronic medical conditions, the complaints or symptoms thus identified are nevertheless of considerable importance for policy making.

CONCLUSIONS

The findings reported here broaden our understanding of the relationship of psychiatric disorders and chronic medical conditions that we reported earlier (15). For example, in the previous paper we reported that persons with cancer had a greater prevalence of recent and lifetime psychiatric disorders. In the current study, however, we found no noticeably greater prevalence of cancer in persons with psychiatric disorders. The likely explanation for the apparent discrepancy is that in a sample drawn from households in the general population, the prevalence of cancer is much lower than the prevalence of psychiatric disorders. Thus, the small contribution to prevalence of psychiatric disorders by persons with cancer has little effect on the overall prevalence of psychiatric disorders. Further, we previously reported no noticeably greater prevalence of psychiatric disorders in persons with diabetes and high blood pressure, yet in the current study we found that persons with any psychiatric disorder have a greater prevalence of both diabetes and high blood pressure. In this case, the explanation is the opposite of that for cancer; the prevalence of both diabetes and high blood pressure is relatively high in the general population. Thus the contribution to prevalence of psychiatric disorders by persons with these conditions is large.

The Epidemiological Catchment Area Program was not designed to determine the cause of the relationship between psychiatric disorders and chronic medical conditions. We suggest that future studies of medical-psychiatric comorbidity in the general population examine the onset and clinical course of specific medical conditions and psychiatric disorders by using prospective designs. Such data are needed to more fully understand the process by which the associations reported here develop over time.

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A Reliability Assessment of the Psychotherapy Supervisory Inventory

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The authors investigated the reliability of the Psychotherapy Supervisory Inventory scales, which rate behaviors of supervisors on the basis of observation of supervision sessions. The scales assess focus on the therapist and the patient, intellectual and experiential orientation, number of clarifying and interpretive comments, intensity of confrontation, depth of exploration, verbal activity level of the supervisor, dominance of the supervisor and the therapist, comfort and tension levels, and empathy of the supervisor. Intraclass correlation coefficients were significant for all scales, indicating that trained observers can agree in distinguishing supervisory behaviors. These scales can be used in further research and for feedback to supervisors.

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There has been little effort to systematically investigate the process of psychotherapy supervision. The classic texts provide a conceptual and theoretical understanding of supervision but are descriptive and anecdotal (1–6). Indeed, research on supervision usually involves reports about the process rather than systematic observation of supervision itself (7–11). To our knowledge, only one other group has looked at videotapes of psychotherapy supervision in an effort to characterize good and outstanding supervision (12). The research reported in this paper is an extension of previous work in which empirically derived dimensions of supervisory behavior were used to describe supervisory styles (13). These dimensions were adapted from the work of Lewis (14), who considered them important in teaching psychotherapy, and were also drawn from experience with psychotherapy supervisors during more than a decade of meetings. We operationalized the dimensions of supervisory behavior and tested whether they can be reliably rated. This paper describes our assessment of the reliability of the scales of the Psychotherapy Supervisory Inventory, which rate supervisory behaviors on the basis of observation of actual supervision sessions with psychiatry residents.

METHOD

The supervisory dimensions and hypothesized styles developed in the previous work were based on observations of tapes of full supervisory hours (13). To refine, operationalize, and test the reliability of these dimensions, we reviewed the original tapes. The original eight dimensions were expanded and made into the 13 scales that make up the Psychotherapy Supervisory Inventory. Four of the original dimensions were split for methodological reasons (so that all dimensions would be scaled identically), and one scale (empathy) was added because of its demonstrated importance in psychotherapy outcome. The definition and labeling of some of the scales were also modified on the basis of group discussions.

Next, we constructed a manual that converted the 13 dimensions into Likert-like scales along with descriptions and examples of each anchor point. Ratings on the scales are made using videotapes of psychotherapy supervision sessions. Only material that is directly related to the patient or the therapist is rated, so that discussion of nonclinical issues is excluded. Ratings are based on the whole videotape rather than a subset of the interaction, since we found that segments of supervision are not fully representative of the process. For instance, at the beginning of a supervision session, the therapist often does a considerable amount of talking, yet he or she may say little later. The scales have 7 points ranging from "little" to "extreme." Seven scales primarily measure the content of the interaction between supervisor and therapist: 1) focus on the therapist, 2) focus on the patient, 3) intellectual orientation, 4) experiential orientation, 5) clarification and interpretation, 6) confrontation, and 7) depth of exploration. Six scales measure interaction relatively devoid of

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content: 1) verbal activity level, 2) dominance of the supervisor, 3) dominance of the therapist, 4) comfort level, 5) tension level, and 6) empathy of the supervisor with the therapist or patient. For purposes of brevity, masculine pronouns will be used for therapists and supervisors throughout the paper, although it is understood that a large number of supervisors and residents are women, and feminine pronouns will be used for patients, even though a large number of patients are men.

The Psychotherapy Supervisory Inventory Scales

The scale for focus on the therapist specifically measures how many of the supervisor's comments are directed to the therapist's feelings, thoughts, and actions. An example is a therapist who expresses concern about a patient who says that she hates her mother. The supervisor who rates high on this scale directs his comments to exploring the resident's concerns rather than the patient's emotional intensities about her mother.

The scale for focus on the patient measures how many of the supervisor's comments are directed to the patient's feelings, thoughts, and actions. Whether or not the comments made about the patient are insightful or empathic or deepen the therapist's understanding of the patient, this scale rates only the amount of the supervisor's discussion of the patient. The supervisor may generalize his comments from the specific patient to other patients, patients in general, or other clinical situations and will still be rated as focusing on the patient. For example, a therapist expresses concern about a patient who says she hates her mother. The supervisor who is rated high on this scale directs his comments to the patient's competitive feelings with her mother and her hostile dependency on her mother. He also discusses dependency. In this instance, there is no acknowledgment of the therapist's reactions to the patient.

The intellectual orientation scale measures the frequency of the supervisor's generalized elaborations, theoretical points, comments on issues of technique, and statements about the patient, patients in general, treatment, or psychiatry. Use of jargon and theory often indicates a highly intellectual orientation, but a high frequency of discursive comments about the therapist or patient is also rated as intellectual. The supervisor who rates high on this scale does not discuss the specific experience of the therapist or patient that is immediate in the presentation. For example, a therapist reports that his patient has requested medication. A supervisor scoring at the low end of the scale might note that this has caught the therapist off guard (relating to the experience of the therapist) or that the patient must be feeling needy (relating to the experience of the patient). A supervisor scoring at the high end of the scale might discuss the indications and contraindications for medication or medication as a transitional object but does not acknowledge the therapist's concerns or relate specifically to the patient.

The experiential orientation scale measures the frequency of the supervisor's comments that emphasize the patient's or therapist's thoughts and feelings as closely as possible to the way they are actually experienced, with little elaboration, generalization, or abstraction. It measures the frequency with which the supervisor stays with the immediate material that the therapist brings to supervision and includes cognitive and affective aspects. An example is a therapist who reports that his patient has complained that her sexual relationship with her lover is losing its excitement. A supervisor who scores low on the scale might comment that this sort of sexual incompatibility occurs when neither partner is able to transcend his or her own narcissistic needs to respond to the partner's needs (an intellectually oriented comment). A supervisor who scores high on the scale might note that the patient is talking about the therapist and invite him to understand her dilemma.

The scale for clarification and interpretation of process rates the frequency of overt interpretive and clarifying statements about either the therapist or the patient. Supervisors with this behavior synthesize and reframe material for the therapist. They put ideas together and describe what is going on. An example of clarifying and interpretive comments is, "This is what I think is going on. It sounds like she makes you feel guilty." A second example is a therapist who reports that his patient feels irritated and does not know why. The supervisor directs the therapist's attention to a comment he made just before the patient became irritated. Another example is a therapist who reports that his patient talked about a man in whom she was interested. The supervisor suggests that the patient might have been talking about the therapist.

The confrontation scale measures the intensity of the supervisor's comments about the therapist's actions, thoughts, and feelings. Confrontational statements range from general comments about the therapist's performance to pointed questions and declarative statements about the therapist's interventions and feelings. An example is a therapist who switches the topic at a difficult moment in the therapy hour. A low rating is given to a supervisor who does not comment on the switch. For a high rating, a supervisor might interrupt the therapist and comment that the therapist likes to switch topics when the patient makes him uncomfortable. The rating is based on the greatest intensity of such comments during the session.

The depth of exploration scale measures the peak moment in the supervisory session where the supervisor aims to deepen the therapist's awareness of what is happening between him and the patient. It is a judgment about the depth to which the supervisor tries to push the therapist to articulate thoughts and feelings about the patient, the relationship, and the patient's dynamics. Although there is some overlap with the focus and experiential orientation scales, this is a specific evaluation of the greatest focus by the supervisor on the therapist's thoughts and feelings. For instance, it is quite possible that a supervisor may not press for depth in exploring the therapist's thoughts and feelings yet focus primarily on the therapist in his comments.

An example of the depth dimension is a therapist who reports having had an uneasy feeling when a patient reviewed the course of her therapy. The patient commented favorably on her improvement and contrasted the way she currently felt with her state of constant suicidal preoccupation before starting treatment. A low rating is given when the supervisor does not explore the therapist's uneasiness, although he may comment, "Yes, your patient seems to be much better than she was 2 years ago." For a very high rating, the supervisor might note that the therapist is uneasy with the patient's feeling better, even though she was suicidal before she entered treatment. The supervisor might note the sense of burden communicated by the therapist and ask to understand what is going on with him. He might even go further and comment on the therapist's ambivalence about being needed and feeling powerful, counterbalanced by worries about the patient's depending on him.

The verbal activity level scale is a global scale that measures the amount of the supervisor's comments throughout the whole session. It measures the duration and frequency of comments rather than the content of comments. A supervisor who has a score at the low end of the scale is quite inactive, whereas a supervisor who is quite active will have a high score.

The dominance scales measure who is in charge of the session, the supervisor or the therapist. They measure more overt behaviors. Who determines what is talked about or initiates a shift in topics is a measure of whether the therapist or the supervisor is dominant.

Dominance of the supervisor is demonstrated in the following example. The supervisor comments to the therapist about possible transference issues. The therapist, feeling inadequate and embarrassed that the supervisor sees things which he does not, acts as though he has made a mistake in therapy. The supervisor then takes time to reassure the therapist that an error has not been made and explains more about transference and its manifestations. When the therapist is calmer and again willing to be introspective, the supervisor returns gently to the transference material.

Dominance of the therapist is evidenced in an instance where, after a few sentences from the tape recorder, the therapist turns off the tape to make a comment.

The climate scales are global assessments of the highest levels of comfort and tension in the session, which tend to ebb and flow. These dimensions do not measure the intensity of tension and comfort over time. Indeed, there may be considerable resolution of tension so that the climate becomes relaxed. The scales measure the highest levels achieved during the session.

A high score on the comfort scale is evidenced by a therapist and supervisor who are sitting comfortably in chairs that are arranged to allow for good eye contact. As they discuss issues concerning the patients, they share in laughter. They are attentive to each other and do not seem to struggle over who will speak next.

A high score on the tension scale is evidenced by a therapist and supervisor who sit far apart, with rigid postures. They seem to struggle rather than collaborate. One or both appear self-conscious, and their tones of voice betray tension and anger.

The empathy scale rates the degree to which the supervisor actively demonstrates his understanding of and affective connection to the patient and therapist. This is conveyed not only by statements in which the content communicates understanding but in the nonverbal aspects of the supervisor's communications. True empathic connection also implies responding accurately to the intensity of the therapist's or patient's feelings. An example is that of a therapist whose voice cracks when he discusses a patient's upcoming termination. A supervisor scoring at the low end of the rating scale ignores this. A supervisor with a score at the high end of the rating scale comments in a kind and warm fashion that he too is going to miss the patient.

Reliability of the Scales

Once the manual had been written and refined, 15 new tapes of 14 different supervisors were obtained. We four authors rated all tapes and were blind to each other's ratings.

Reliability of the ratings was assessed using the intraclass correlation coefficient (ICC) and Finn's index. The ICC compares variance between subjects to variance within subjects and is the most widely accepted measure of interrater reliability (15–17). It is sensitive to skewness and can be low if there is a small variance between subjects. For example, this was noted on the patient focus scale, since most supervisors talk a great deal about residents' patients and thus score high on this scale. Addressing this problem, Whitehurst (17) proposed Finn's index (r_F) as an alternative measure. This measure compares the variance within subjects to the variance of ratings that would be predicted by random ratings. A Finn index higher than the ICC indicates that there is less variability in the ratings and more agreement between raters. Statistical significance was determined by analysis of variance. The reliabilities for the mean scores of two and four raters are also reported (15, pp. 127, 131). These are interpreted to mean that if another random sample of raters were to rate the same subjects, the reliability coefficient would be the correlation between the two sets of data. This is known as the Spearman-Brown intraclass correlation coefficient (15, p. 128; 18).

RESULTS

The interrater reliabilities are reported in table 1. All of the ICCs were statistically significant: for 11 scales at 0.0001, for tension level at 0.01, and for comfort

TABLE 1. Interrater Reliability on Scales of the Psychotherapy Supervisory Inventory

Scale	ICC[a] (df=14, 45)	r_F[b]	r_2[c]	r_4[d]
Focus on therapist	0.62[e]	0.71	0.76	0.87
Focus on patient	0.46[e,f]	0.85	0.63	0.78
Intellectual orientation	0.43[e]	0.79	0.60	0.75
Experiential orientation	0.49[e]	0.54	0.66	0.79
Clarification and interpretation	0.60[e]	0.74	0.75	0.86
Confrontation	0.64[e]	0.72	0.78	0.88
Depth of exploration	0.58[e]	0.72	0.73	0.85
Verbal activity level	0.50[e]	0.80	0.67	0.80
Dominance of supervisor	0.60[e]	0.83	0.75	0.86
Dominance of therapist	0.52[e]	0.78	0.68	0.81
Comfort level	0.22[g]	0.60	0.36	0.53
Tension level	0.27[h]	0.52	0.42	0.59
Empathy of supervisor	0.56[e]	0.73	0.72	0.84

[a] ICC=intraclass correlation coefficient.
[b] r_F=Finn's index.
[c] r_2=Spearman-Brown intraclass correlation coefficient, two raters.
[d] r_4=Spearman-Brown intraclass correlation coefficient, four raters.
[e] $p=0.0001$.
[f] df=13, 42.
[g] $p=0.03$.
[h] $p=0.01$.

level at 0.03. Finn's index was higher than the ICC for all scales.

With respect to the patient focus scale, we discovered a confusing element in our original definition of how to rate a supervisor's generalizations about patients. After discussion, it was decided that a supervisor's frequent comments about patients in general would result in a high rating on the patient focus scale. This affected three tapes in which supervisors made these kinds of comments extensively. One tape was used for discussion, and two tapes were rerated and the interrater reliability for the scale recalculated. The old values for the patient focus scale (ICC=0.35, $p=0.002$; $r_F=0.74$) were slightly lower than the new values (table 1).

DISCUSSION

This research revealed that trained observers can reach considerable agreement in distinguishing various supervisory behaviors. The scales can now be used in further research by other investigators. We recommend that at least two individuals rate each tape, since this increases reliability.

Throughout the construction of the scales, the raters had difficulty agreeing on ratings of comfort and tension. These scales were kept in the inventory in order to assess the magnitude of such disagreement. Interestingly, interrater reliability on these scales was significant. Assessment of comfort, however, showed a lesser level of agreement than assessment of tension. A likely explanation is that tensions are often hidden. Supervisor and therapist accommodate to each other over time, so that tensions are not easily revealed. The ratings reflect these accommodations.

The Psychotherapy Supervisory Inventory provides a format for systematic feedback to psychotherapy supervisors. If supervisors are clearer about their patterns of interaction with the therapists, they have the potential for changing their behaviors. In view of the high level of observer agreement about various supervisory behaviors, the research also has implications for educational policy. Perhaps periodic review of videotaped supervision sessions by skilled observers and feedback to supervisors should be a prerequisite for doing supervision. Future research will lend weight to this possibility.

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ECT and Parkinson's Disease Revisited: A "Naturalistic" Study

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In an open study, seven patients with Parkinson's disease received ECT for major depression. Both the motor dysfunction and the mood impairment of these patients improved following an average of seven ECT sessions. Significant improvement in motor function occurred after only two treatments. All aspects of Parkinson's disease improved significantly after ECT. Older patients showed greater improvement in motor function. The authors conclude that the therapeutic utility of ECT in depressed and nondepressed patients with Parkinson's disease should be further evaluated.

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For many years ECT has been used to treat depressed patients with Parkinson's disease who are resistant to antidepressant medication. It has been noted that ECT improves not only the depressed mood but also the motor impairment in Parkinson's disease (1–9). Recently, two reports (10, 11) demonstrated a significant improvement in Parkinson's disease in association with ECT treatment of mania. Balldin et al. (12) reported a marked improvement of motor function in five out of seven patients who had received ECT for their depression. Moreover, Andersen et al. (13) successfully treated 11 patients with Parkinson's disease with on-off phenomena. In contrast, Ward et al. (14) did not find ECT useful in patients with Parkinson's disease with on-off phenomena. Young et al. (15) suggested that ECT may have a specific therapeutic effect on parkinsonism independent of its effect on depression. A major theme addressed in many of these reports is the relationship of the effect of ECT on affective and motor symptoms. Some authors (1, 14, 16) felt that motor improvement is secondary to changes in affect; others (5, 12, 15) suggested that ECT has independent effects on the two systems.

A direct therapeutic effect of ECT on Parkinson's disease seems plausible on neurochemical grounds. Several studies (16–19) support a synergistic interaction between dopamine agonists and electroconvulsive shock. Reserpine-pretreated rodents (i.e., rodents with parkinsonism induced by catecholamine depletion) (19, 20) manifest improvement in motor function following electroconvulsive shock. Repeated administration of electroconvulsive shock enhances the responsiveness of the central dopamine and norepinephrine structures to levodopa and direct dopamine agonists (18, 19). Also, ECT increases the permeability of the blood-brain barrier, thereby augmenting drug concentration in the human brain (9, 21).

In this paper we will report the effects of ECT on parkinsonian and affective symptoms in seven depressed patients with Parkinson's disease.

METHOD

The study included seven depressed patients with Parkinson's disease (five men and two women) who were 61–73 years old (mean±SD age=67±4 years). The patients had been diagnosed and followed for an average of 9 years by neurologists not associated with this study. The instrument used to measure motor function was the New York University Parkinson's Disease Scale, which was developed at New York University by Lieberman et al. (22). It is a 100-point scale with five major subscales: rigidity, tremor, bradykinesia, gait, and postural stability. Each of these subscales accounts for a maximum of 20 points on the scale.

All patients had bilateral motor impairments; one patient had stage 5, five had stage 4, and one had stage 3 Parkinson's disease. Combination doses of carbidopa (ranging from 30 to 200 mg/day) and levodopa (ranging from 200 to 2000 mg/day) were held constant throughout the trial. All patients met *DSM-III* criteria for major depression, which developed during the course of parkinsonism; three of the seven patients were suicidal (patients 1, 3, and 6), and all had scores higher than 20 on the Hamilton Rating Scale for De-

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TABLE 1. Change in New York University Parkinson's Disease Scale Scores of Seven Patients Treated With ECT and a Carbidopa-Levodopa Combination

Patient	Age (years)	Sex	Pre-ECT Score	Change in Score After Second ECT (%)	Change in Score After Fourth ECT (%)	Change in Score After All ECT (%)	Doses of Carbidopa and Levodopa (mg/day)
1	68	Female	79	−8	−46	−46	200, 2000
2	71	Male	68	−24	−6	−60	100, 1000
3	68	Male	61	−74	−75	−74	100, 1000
4	61	Male	51	−41	−65	−41	50, 500
5	62	Male	36	—[a]	−72	−39	40, 400
6	65	Male	95	−16	−38	−21	150, 1500
7	73	Female	65	−43	−46	−80	30, 300

[a] Scale not administered to this patient after second ECT.

pression. A 21-item Hamilton depression scale was used, and patients had a mean±SD total score of 27±4 points (range=21–33). All patients signed informed consent forms.

The determination of need for ECT was made clinically by the patient's primary psychiatrist after the patient had failed to respond to an adequate trial of antidepressant drug therapy. The ECT machine was a Mecta model SR-1 with bidirectional square-wave pulse and a single channel recorder for EEG or ECG. The patients received an average of seven bilateral ECT sessions. For the group as a whole the initial mean±SD ECT measures were 56±9 Hz for the pulse frequency, 1.5 msec for the pulse width, and 1.46±0.33 seconds for the stimulus duration. The dose of electrical charge was adjusted (23) up to a mean maximum of 76±9 Hz for the pulse frequency, 1.6±0.2 msec for the pulse width, and 1.6±0.22 seconds for the stimulus duration. Every patient received enough electrical charge just above the seizure threshold to produce an adequate seizure duration of 30 to 45 seconds (23). Because patients with Parkinson's disease have a proclivity to develop dementia or confusion (24), we used a just-above-threshold dosing approach. Since there is no information about seizure threshold in Parkinson's disease, the initial ECT measures were determined according to sex and age in order to be as close as possible to the threshold of these patients (23). Patients 2 and 3 had short seizures (i.e., less than 15 seconds) for the first two to four sessions. However, they subsequently seized after double stimulation on maximum settings. Patients were pretreated with either 0.2 mg of glycopyrrolate or 0.4 mg of atropine, 60–80 mg of methohexital, and 40–80 mg of succinylcholine given intravenously by an anesthesiologist.

Patients were rated with the Hamilton depression scale and a modified version of the New York University Parkinson's Disease Scale (22) at baseline; 24 hours after the second, the fourth, and the last ECT; and, finally, 72 hours after the last ECT. Six patients (not patient 5) were rated for motor improvement after the second ECT. The raters were not blind to the fact that patients were receiving ECT.

A one-factor repeated measures analysis of variance (ANOVA) was used to examine the main effect of ECT on Parkinson's disease scale scores, and the Fisher planned least significant difference was performed to compare Parkinson's disease scale scores at baseline, after the second, after the fourth, and after the last ECT. We do not have a Parkinson's disease scale score after the second ECT for patient 5. In order to retain this patient in the statistical analysis we made a conservative estimate by using the baseline Parkinson's disease scale score, assuming that it was unchanged after the first two ECTs. It should be noted that for all the other patients the Parkinson's disease scale scores had improved after the second ECT. Pearson's correlation tests were conducted to study relationships between age, dose of levodopa or years of levodopa therapy, and changes of motor function after treatment. Two-tailed paired t tests were used to study differences in all five Parkinson's disease scale subscale scores before and after ECT.

This study was approved by the Subcommittee for Human Subjects at the New York Veterans Administration Medical Center and the Institutional Review Board at New York University Medical Center.

RESULTS

Individual scores for motor changes are shown in table 1. The patients' mean scores on the New York University Parkinson's Disease Scale subscales are presented in table 2.

The mean±SD pretreatment scores on the New York University Parkinson's Disease Scale and the Hamilton depression scale in this group of patients were 65±15 and 27±4, respectively. This group had an average of stage 4 Parkinson's disease with severe depression and no severe cognitive impairments (the patients scored an average of 28 points in the Mini-Mental State examination [25]).

A one-factor repeated measures ANOVA showed a main antiparkinsonian effect of ECT ($F=13.48$, df=3, 18, $p<0.0001$). The mean±SD baseline Parkinson's disease score (65±15) was significantly higher than all subsequent scores, and the mean Parkinson's disease score after the second ECT was significantly higher than the score at end of treatment ($p<0.05$, Fisher

TABLE 2. New York University Parkinson's Disease Scale Motor Subscale Scores of Seven Patients With Parkinson's Disease Before and After ECT

Subscale	Before ECT Mean	Before ECT SD	After ECT Mean	After ECT SD	Change (%)	t[a] (df=6)	p
Rigidity[b]	14.0	4.7	6.0	4.0	–57	–7.3	<0.001
Tremor[b]	9.0	4.3	4.0	4.3	–56	2.8	<0.05
Bradykinesia[b]	15.0	4.5	9.3	4.5	–38	–3.4	<0.05
Gait[b]	11.4	5.3	5.7	5.3	–50	–2.8	<0.05
Postural stability[b]	14.2	3.9	7.1	3.9	–50	4.8	<0.001
Total[c]	65.0	15.0	32.0	6.0	–51	5.9	<0.001

[a] Two-tailed.
[b] Maximum possible score=20.
[c] Maximum possible score=100.

planned least significant difference). However, the Parkinson's disease score after the fourth ECT was not significantly higher than the score at the end.

All five aspects of Parkinson's disease (i.e., rigidity, tremor, bradykinesia, gait, and postural stability) responded equally to ECT (table 2).

Patients 1 and 6 developed severe dyskinetic movements of the mouth and choreiform movements of the limbs and body after the last ECT. The dyskinesia disappeared after their combination doses of carbidopa and levodopa were cut in half.

All patients were followed clinically by their primary physician. Patients 1 and 2 relapsed after 6 and 4 weeks, respectively; patients 3, 4, 5, and 7 remained improved after 6 months; and patient 6 had minimal improvement but remained disabled even after the ECT treatment.

Only four of the seven patients were rated for mood changes after their baseline Hamilton depression scale. Patients 1 and 6 did not speak English, and the same interpreter was not available for every testing session. Patient 3 had severe hearing problems that rendered the interviews difficult. Nevertheless, mood improved clinically in all patients after ECT. For those who had a final Hamilton depression scale rating, the score changes were –27%, –52%, –43%, and –80% for patients 2, 4, 5, and 7, respectively. After the fourth ECT, the first point at which a comparison could be made between mood changes and motor changes, there was similar improvement in patients 4 (depression score change=–57% and Parkinson's disease score change=–65%) and 7 (depression score change =–31% and Parkinson's disease score change= –46%), a much greater improvement in mood in patient 2 (depression score change=–52% and Parkinson's disease score change=–6%), and a much greater effect on Parkinson's disease in patient 5 (depression score change=–34% and Parkinson's disease score change=–72%). The Parkinson's disease scale data are shown in table 1.

Patients 1, 2, and 6 got confused after the last ECT, but the delirium cleared before the last rating session for patient 2. In patients 1 and 6 this ECT-induced confusion cleared after 3 days.

Consistent with the findings of Balldin et al. (7, 12) and Andersen et al. (13), we found a robust and positive correlation between age and differences between Parkinson's disease scale scores at baseline and at the end of ECT treatment ($r=0.917$, $df=5$, $p<0.001$): older patients had the greatest improvement. However, dose of levodopa (957±624 mg; range=300–2000 mg; $r=0.01$, $df=5$, n.s.) and number of years the patients had been taking levodopa (7±3.4 years; range=6–10; $r=-0.264$, $df=5$, n.s.) did not correlate with treatment response.

DISCUSSION

ECT improves Parkinson's disease early in the course of therapy. We found significant improvement in motor function in five patients (patients 2, 3, 4, 6, and 7) after only two treatments. Also, we noted clinical benefit in all motor aspects of Parkinson's disease—rigidity, tremor, bradykinesia, gait, and postural stability. Two of the patients who responded to ECT developed dyskinesias that ceased after their dopaminergic drug doses were reduced. This may be further evidence of the impact of ECT on dopaminergic mechanisms or on the permeability of the blood-brain barrier (9, 21). In this study the duration of improvement was variable, and the patients who developed delirium during the treatment relapsed early. According to a Swedish group (7, 12, 13), the benefits are transient. However, in 1985 Baruch et al. (26) reported that four out of six patients experienced 3–8 years of remission. Further characterization of the patients with recurrent symptoms is needed to predict treatment response and to design maintenance therapy strategies.

The antiparkinsonian effects of ECT may be mediated by multiple neurochemical systems. The involvement of dopaminergic pathways is supported by both preclinical and clinical studies. Repeated electroconvulsive shock increases dopamine transmission in animals (17–20). Isaac et al. (27) reported increased endogenous monoamine oxidase inhibitor activity in both the brain and the CSF of cats following chronic electroconvulsive shock, suggesting a potential mechanism that may enhance dopamine transmission. In addition, increased opioid system function has been implicated in the pathophysiology of Parkinson's disease (28), and it is known that chronic electroconvulsive shock reduces striatal opiate receptor activity (29). This in turn increases striatal and mesolimbic dopamine release (30), implying that the effects of ECT on opiate receptors may play a role in the modulation of dopamine transmission.

Despite strong evidence of the influence of electroconvulsive shock on the dopamine system in animals, some issues remain controversial in humans. Successive ECTs greatly reduce prolactin release (31) and also increase CSF homovanillic acid (HVA) in depressed patients (32, 33), suggesting enhanced dopaminergic tone. However, levels of CSF HVA fail to change after ECT in patients with Parkinson's disease (13). Our study suggests that changes in Parkinson's disease occur very early in the course of ECT in some patients. Thus, there may be an initial surge of dopamine turnover following the first two ECTs in this selective group of patients, who may have some degree of dopaminergic neuronal plasticity and who therefore may respond to ECT. This early surge may not be reflected by CSF HVA levels at the end of a full trial of ECT.

ECT-increased dopamine receptor sensitivity remains the most accepted hypothesis to date (34, 35). The effects of ECT on prolactin secretion reflect dopamine D_2 receptor activity (36), but a selective increase of D_1 receptor activity in rodents has been suggested (35, 37). We have confirmed the finding of increased D_1 function in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (Sershen et al., 1989 unpublished data). It has been suggested that D_1 receptor stimulation facilitates D_2-mediated effects (36). However, trials of a D_1 dopamine agonist, SK 38393, have been unsuccessful in patients with Parkinson's disease and monkeys whether administered alone or with L-dopa (36, 38, 39). It is possible that SK 38393 behaves as a D_1 antagonist in some patients or may not attain adequate concentration in the brain tissues (36). If administered with ECT these problems may be overcome.

Further studies designed to clarify the mechanisms of ECT's effects on Parkinson's disease should focus on CSF monoamine metabolite levels and on in vivo imaging of brain receptors to elucidate the role of D_1 and D_2 activities.

We also noted significant affective improvement in our subjects with Parkinson's disease, in keeping with numerous reports (1–8). The therapeutic mechanisms of ECT in depression are unknown, but they are thought to involve adrenergic, serotonergic, and other transmitter pathways (40). It is unclear whether the antidepressant effects of ECT in patients with Parkinson's disease occur through similar or unique neurochemical circuits.

Disagreement exists as to the causal relationship of mood improvement to motor change after ECT in depressed subjects with Parkinson's disease. Affective improvement is uncommon after the second ECT (41), although this time course has not been established in parkinsonian patients specifically. Thus, further work should focus on motor and affective measures after the first two treatments in patients with Parkinson's disease. We did see a dissociation of antidepressant and antiparkinsonian effects in two out of four subjects in whom this comparison was possible (patients 2 and 5). Patient 5 demonstrated a significant motor response despite an actual setback in mood after four ECTs.

We found a significant correlation between age and response of motor symptoms to ECT. The fact that older patients responded better than younger ones may be another aspect of the differences between early- and late-onset Parkinson's disease. These differences include a more rapid decline, diminished responsiveness to dopa treatment, and greater susceptibility to the development of dementia in older patients with Parkinson's disease (24). It is unclear why ECT would be more beneficial for these patients.

ECT improves mood and motor symptoms in depressed patients with Parkinson's disease. The marked responsivity of the motor symptoms suggests that the utility of ECT should be further evaluated in both depressed and nondepressed patients with Parkinson's disease as a potential treatment in the following conditions: 1) movement disorder unresponsive to increased doses of dopa or an inability to tolerate a dose increase and 2) psychotic disturbances necessitating a decrease in medication plus antipsychotic treatment.

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The Role of Social Relationships in the Course of First-Episode Schizophrenia and Affective Psychosis

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The Markers and Predictors of Psychosis study at the University of British Columbia addresses the role of psychosocial factors, such as social relationships, in predicting the short-term course of first-episode schizophrenia. Before their first episode of illness, schizophrenic subjects had fewer and less satisfactory social relationships than subjects with affective psychosis and a matched, normal comparison group. Nonfamily social resources were positively associated with good prognosis for both psychotic groups. While involvement with family members also predicted good prognosis among subjects with affective psychosis, family involvement had a negative association with outcome among schizophrenic subjects.

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Findings suggesting that the course of schizophrenia is more favorable in developing than in industrialized countries (1–3) have stimulated investigations of sociocultural factors that might affect prognosis. While the supposedly greater availability of social support in developing as opposed to industrialized countries has been cited as one possible explanation for these findings (4), empirical investigations of the role of social factors in predicting the course of psychotic illness have been surprisingly limited. The current investigation of the role of social relationships in predicting outcome after an initial episode of illness is part of the University of British Columbia Markers and Predictors of Psychosis study, a prospective longitudinal study of schizophrenia and affective psychosis.

Population surveys and research with clinically identified populations suggest that good social relationships help to maintain mental health (5–12). Several authors have made a conceptual distinction between the qualitative and quantitative aspects of interpersonal relationships that contribute to mental health (13, 14). The number of friends and relatives, also called social resources or the social network, has been differentiated from social support, which refers to the way in which an individual perceives his or her interpersonal relationships. Social support is always positive: It is the degree to which one is satisfied with the current social network (14). While social support is, by definition, positive, the effect of social resources is more equivocal. For example, while the social network generates a potential for social support, demanding or intrusive members in a network may create psychological stress.

The few published studies of the interpersonal relationships of schizophrenic patients deal with the social network, not social support. These studies suggest that schizophrenic patients have smaller networks than normal subjects, medical patients, or other nonpsychotic psychiatric patients (15–20). Persons with depressive disorders also have smaller networks than are found in the general population (21). The composition of social networks has also attracted attention. Two studies (15, 16) have reported that family members dominate the relationships of schizophrenic patients, whereas normal subjects are more likely to be involved with both family and friends.

Only one study has related social network to prognosis. From a retrospective study of chronic schizophrenic patients, Cohen and Sokolovsky (18) concluded that social network variables do affect course of the disorder but only among the mildly impaired. To our knowledge, no study of schizophrenia or of affective psychosis has directly tested the hypothesis that quantitative or qualitative aspects of interpersonal relationships are prognostically significant in the course of recovery after the first episode of illness.

The current report examined the social relationships of persons suffering a first episode of schizophrenia or affective psychosis and compared them with social re-

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lationships of a matched, normal comparison group. Analyses also focused on the association between social relationships and outcome 18 months later.

METHOD

Data for this study were drawn from two groups: 175 persons experiencing an episode of psychosis for the first time in their lives and a comparison group of 122 normal volunteers. A complete description of project participants, the referral network, and inclusion and exclusion criteria can be found elsewhere (9, 22).

Psychiatric subjects were recruited from a far-reaching referral network that was designed to identify residents of Greater Vancouver who were experiencing a first lifetime episode of psychosis. To ensure that the maximum number of potential subjects were identified, we specified broad inclusion criteria, namely, either one or more psychotic symptoms (hallucinations, delusions, thought disorder, or marked change in behavior) or two or more of the following symptoms: reduction or loss of interest, reduced initiative and drive, deterioration in performance, social withdrawal, or persistent self-neglect.

Of 300 potential subjects identified, 175 signed a consent form to participate in the study. Ninety-four of the persons referred (31.3%) refused to participate, and an additional 31 (10.3%) either had moved out of the area or had disappeared from the treatment system before they could be contacted. Analyses comparing participants with the potential subjects lost to the study revealed no age or sex differences.

In an effort to avoid the socioeconomic bias associated with using undergraduate volunteers (the most frequent source of normal comparison groups), we recruited subjects from employment centers, the Young Men's Christian Association, a union hall, family practices in low-income neighborhoods, and technical, vocational, and community colleges. Quota sampling was employed in order to match normal recruits with psychotic subjects on age and sex. Each subject was asked to recruit at least one significant other—a family member or close friend—to provide ancillary data and to aid in tracking our subjects during follow-up.

At both intake and follow-up 18 months later, a psychiatrist or clinical psychologist administered the Present State Examination (23) to each member of the psychiatric group. At both times, trained lay interviewers obtained collateral information from the significant other, as well as from clinical or hospital records. In the interview at 18 months, extensive data were also obtained regarding treatment, medication, work or school performance, living situation, and extent of socializing during the follow-up interval. Case conferences produced "best estimate" (24) consensus psychiatric diagnoses, a procedure that optimizes reliability when complex data are considered (25, 26).

During the first contact with a research subject, we administered the Interview Schedule for Social Interaction (27, 28). The schedule inquires about three categories of interpersonal relations.

Social network constitutes the first dimension. The respondent is asked to list all family and friends whom he or she is "close to, fond of, or attached to," or people on whom he or she counts for emotional or material support. These people are coded as either kin (immediate or extended family) or nonkin.

The second dimension, the availability of social resources, is a measure of number of contacts with family, friends, and casual acquaintances. Availability is divided into two subscales: 1) close and confiding relationships (e.g., "the number of people with whom you share your most private feelings") and 2) acquaintances (e.g., "people whom you know just a little, who would do small favours for you").

The third category inquires about social support from two sources: close and confiding relationships and acquaintances. A sample item from the scale that assesses the adequacy of close and confiding relationships is: "Regarding the people with whom you share your most private feelings: would you like to share more, or less, or is it about right for you?" An example from the adequacy of acquaintances scale is: "Would you like more or fewer people to do small favours for you, or are you currently satisfied?" (A complete copy of the four scales derived from the Interview Schedule for Social Interaction is available from Mr. Erickson on request.)

Since the responses to items used within each of the two availability and two adequacy scales are expressed in different metrics, we transformed raw values into standardized scores by calculating the mean and standard deviation for each item, on the basis of the value obtained from the normal comparison group. The four scale values were derived from the sum of the standardized item values: Thus, the mean for the normal group was about zero. Mean values on these four scales for the psychotic groups are expressed in standard deviation units, relative to the value obtained from the normal group.

The four scales possess good formal properties. Cronbach's alpha coefficients, when computed separately for the patients with schizophrenia or affective psychosis and the normal subjects, ranged from 0.60 to 0.92. Two-thirds of the coefficients were higher than 0.70.

Socioeconomic status was assessed by an index developed by Blishen and colleagues on the basis of Canadian norms (29, 30). Scale scores, derived from a weighting of education and income, range from 15 to 85. Separate norms exist for men and women.

Adaptive functioning is becoming an increasingly important component of clinical assessment (31–35). In this study, the *DSM-III* axis V rating, which measured the highest level of social and occupational functioning in the 9 months leading up to the follow-up interview, was selected as the outcome measure. Axis V ratings at intake, referring to the year before admission to the study, provided a baseline measure of func-

TABLE 1. Intake Ratings of Social Resources and Perceived Social Support for Subjects With First-Episode Schizophrenia or Affective Psychosis and for Normal Volunteers

Measure (from Interview Schedule for Social Interaction)	Rating[a]: Schizophrenic Subjects (N=63) Mean	SD	Affective Psychosis Subjects (N=55) Mean	SD	Normal Volunteers (N=122) Mean	SD	F	df[b]	p
Social resources									
Availability of close and confiding relationships[c]	−4.5	2.9	−1.0	5.3	0.0	3.9	24.0	2, 214	0.001
Availability of acquaintances	−1.8	9.0	0.1	7.7	0.1	4.4	1.7	2, 222	n.s.
Perceived social support									
Adequacy of close and confiding relationships	−1.4	3.7	−0.6	4.5	0.0	3.8	2.5	2, 220	0.10
Adequacy of acquaintances	−1.6	3.8	−0.3	3.7	0.1	3.4	4.3	2, 223	0.05

[a] Scale values derived from sum of standardized item scores, with distribution of item scores from normal comparison group used as basis for transformations (see text for full explanation).

[b] Degrees of freedom vary slightly because of pairwise deletion of missing data.

[c] Significant difference between schizophrenic patients and other two groups ($p<0.05$, Student Newman-Keuls test).

tioning. In a test of interrater reliability of axis V ratings, the correlation (r) between independent ratings made by two project clinicians was 0.89. In an earlier report (10), we described how axis V ratings at intake, used as an operational definition of premorbid social and occupational functioning, successfully differentiated schizophreniform and schizophrenic subjects.

RESULTS

Sample Characteristics

Most of the 175 psychotic subjects received a *DSM-III* diagnosis of schizophrenia (N=72) or affective disorder with psychotic features; the latter group comprised bipolar (N=44) and major depressive (N=30) disorders. The remaining subjects, who had diagnoses of schizophreniform (N=9), schizoaffective (N=7), paranoid (N=7), and other (N=6) psychoses, were not considered in this report. Most of the subjects were young (mean±SD age=25.2±8.1 years, range=15–50). Three-quarters had not yet reached their thirtieth birthday. Males outnumbered females by a ratio of two to one.

The normal subjects were slightly better educated than the psychotic subjects: While 63% (N=77) of the normal subjects had completed high school, this was true for only 44% (N=77) of the psychotic group ($\chi^2=8.80$, df=1, $p<0.005$, with Yates' correction). Ratings of parental occupation, which used the Blishen scale, suggested that the psychotic group came from a lower socioeconomic background than the normal group (mean±SD scores=45.2±15.0 for the psychotic group and 55.0±14.3 for the normal group; t=−5.49, df=281, $p<0.001$).

At the 18-month follow-up, we successfully reinterviewed 73% (N=127) of the psychotic group and 71% (N=87) of the normal comparison group. Dropouts were slightly older than those who remained in the study (mean±SD ages=27.5±9.1 versus 24.4±7.6 years, respectively; t=2.26, df=173, $p<0.05$). Dropouts also came from a somewhat lower socioeconomic background than those who remained in the study (mean±SD parental Blishen scores=41.6±15.6 versus 47.4±15.1; t=−2.07, df=150, $p<0.05$). Dropouts were equally distributed among the schizophrenic and affective disorder categories.

Social Relationships

Comparisons of the size and composition of the social networks at the beginning of the study revealed a gradient, with schizophrenic subjects tending to identify the least number of friends (3.6±3.1), normal volunteers the most (6.3±4.6), and persons with affective psychosis falling in between (5.0±4.7) (F=7.8, df=2, 237, $p<0.001$). Differences between the schizophrenic and normal groups were statistically significant ($p<0.05$, Student Newman-Keuls post hoc test). Although differences in numbers of family members in the social networks of each of the three groups did not reach conventionally accepted levels of statistical significance, there was a trend suggesting that, in comparison with the other two groups, schizophrenic subjects identified fewer family members (schizophrenic subjects=3.7±2.7, affective psychosis subjects=4.4±3.2, normal volunteers=4.6±2.9; F=2.1, df=2, 237, $p<0.10$).

Table 1 presents comparisons of social resources and perceived social support among the three groups. Schizophrenic subjects had fewer close and confiding relationships than subjects with affective psychosis and normal volunteers, but there were no group differences in the availability of acquaintances. There were differences in the adequacy of perceived social support from acquaintances; however, no two groups were significantly different. A nonsignificant trend ($p<0.10$) was

TABLE 2. Correlations Between 18-Month Axis V Ratings[a] and Social Relationship Variables, Intake Level of Functioning, and Demographic Characteristics for Subjects With First-Episode Schizophrenia or Affective Psychosis

Item	Correlation With 18-Month Axis V Rating[a] (Pearson zero-order correlation): Schizophrenic Subjects (N=46)[b]	Correlation With 18-Month Axis V Rating[a] (Pearson zero-order correlation): Affective Psychosis Subjects (N=49)[b]
Social resources		
Availability of close and confiding relationships	0.17	0.07
Availability of acquaintances	0.25[c]	−0.14
Perceived social support		
Adequacy of close and confiding relationships	0.07	0.08
Adequacy of acquaintances	0.35[d]	−0.01
Social network		
Number of family	−0.25[c]	0.18
Number of friends	0.37[d]	0.38[d]
Intake level of functioning		
Intake axis V rating	0.38[d]	0.50[d]
Demographic characteristics		
Age	0.13	0.27[c]
Sex (1=male, 2=female)	0.18	0.28[c]
Socioeconomic status	0.00	0.19

[a] While the usual scale for *DSM-III* axis V ratings is from 1 (best) to 7 (poorest), the direction of the scale has been reversed to aid interpretation. Here, higher values indicate higher levels of social and occupational functioning.

[b] Sample sizes are reduced because of listwise deletion of missing data.

[c] $p<0.05$.

[d] $p<0.01$.

present with respect to the adequacy of close and confiding relationships.

Prediction of Outcome at 18 Months

Do social network, social resources, and perceived social support predict recovery from psychotic illness? Eighteen months after intake, schizophrenic subjects had significantly worse axis V mean scores than subjects with affective psychosis (mean±SD=3.2±1.1 versus 4.3±1.2; $t=-4.8$, df=116, $p<0.001$). Even though, on the whole, schizophrenic subjects functioned at a worse level at 18 months than persons with affective psychosis, standard deviations in both groups were equal, suggesting comparable variability of adaptive functioning within the two groups.

In general, correlations between predictor variables and 18-month axis V ratings provided strong support for the hypothesis that greater involvement with and higher quality of social relationships make for better prognosis in schizophrenia. Table 2 shows that four of six variables that assess social relationships were significantly correlated with 18-month outcome. Of the two measures of perceived social support, only the adequacy of acquaintances related significantly to outcome for schizophrenic subjects. The relationship between the number of kin in the network and outcome was opposite to the study hypothesis: The correlation of −0.25 indicates that greater numbers of kin were associated with *poorer* rather than better prognosis for schizophrenic subjects. For both diagnostic groups, however, the number of nonfamily members within the social network was significantly associated with a positive axis V rating. Social relationships were less strongly associated with outcome among subjects with affective psychosis: Only one of the six relationship variables had a significant correlation with 18-month outcome.

Table 2 also examines the contribution of several other variables to the level of functioning. As expected, intake axis V ratings were highly correlated with 18-month outcome for both groups. Being older and being female were significantly related to positive outcome in the group with affective psychosis.

To control for any shared variance among the predictor variables, we conducted a hierarchical regression analysis, using 18-month axis V ratings as the dependent variable. In step 1 the intake axis V ratings were entered, followed by the subject's age and sex at step 2, and diagnostic group at step 3. In step 4 the social relationship variables were added to the equation. In the last step we added terms representing the interaction of diagnostic group with social relationship variables. With the variables entered in this order, we set a highly stringent test of the effect of social relationships. We wished to determine whether relationships make a unique contribution to outcome *after* traditional predictors such as age, sex, diagnosis, and level of premorbid functioning are controlled. Table 3 presents the results of these analyses.

The first step, the intake axis V rating, accounted for 29% of the variance in outcome (adjusted $R^2=0.29$). In step 2 the addition of age and sex resulted in a significant increase in R^2 (R^2 change=0.09, F change=6.28, $p<0.01$): Age and sex each made a significant independent contribution, after the previous level of functioning was controlled. In step 3 the addition of diagnostic group to the equation did not improve the prediction (F change=2.67, n.s.), indicating that the better prognosis of subjects with affective psychosis is an artifact of different age, gender distribution, and adaptive functioning within the diagnostic groups before onset of illness.

The addition of the social relationship variables further increased the prediction of outcome, to a multiple R of 0.68. Even with demographic and diagnostic variables controlled, social relationships accounted for an additional 7% of the variance in 18-month axis V ratings. Of the four variables added at step 4, the number of nonkin in the social network made the only statistically significant contribution.

Up to this point, the prediction examined outcome for both diagnostic groups combined. Step 5, an analysis of interaction terms, showed that the availability of acquaintances and the number of kin in the network operated in different ways for the two diagnostic groups. Table 2 indicates that the correlations between the availability of acquaintances and outcome were

TABLE 3. Hierarchical Regression Analysis Predicting 18-Month Outcome of Subjects With First-Episode Schizophrenia or Affective Psychosis[a]

	Step 1		Step 2		Step 3		Step 4		Step 5	
Variable Entered in Step	Beta	T	Beta	T	Beta	T	Beta	T	Beta	T
1. Intake axis V rating	0.54	6.15[b]	0.49	5.78	0.42	4.60	0.37	3.98	0.41	4.50
2. Demographic characteristics										
Age			0.17	2.08[c]	0.16	1.88	0.17	2.03	0.15	1.89
Sex (1=male, 2=female)			0.22	2.67[b]	0.20	2.38	0.18	2.20	0.17	2.08
3. Diagnostic group (1=schizophrenic, 2=affective psychosis)					0.15	1.63	0.14	1.49	−0.16	−0.84
4. Social relationships										
Availability of acquaintances							−0.03	−0.38	0.62	2.62
Adequacy of acquaintances							0.07	0.81	0.25	0.94
Number of kin in network							−0.10	−1.17	−0.70	−2.54
Number of nonkin in network							0.25	2.92[b]	0.30	0.81
5. Interaction terms										
Diagnosis by availability of acquaintances									−0.72	−2.98[b]
Diagnosis by adequacy of acquaintances									−0.27	−1.03
Diagnosis by number of kin in network									0.76	2.35[c]
Diagnosis by number of nonkin in network									−0.09	−0.21

[a] In hierarchical regression analysis, individual variables are tested for significance only at the step at which they are entered. Overall stepwise statistics—multiple R, R^2 change, and F change—are as follows: step 1: 0.54, 0.29, and 37.77 ($p<0.01$); step 2: 0.61, 0.09, and 6.28 ($p<0.01$); step 3: 0.63, 0.02, and 2.67; step 4: 0.68, 0.07, and 2.65 ($p<0.05$); and step 5: 0.73, 0.08, and 3.49 ($p<0.01$).

[b] $p<0.01$.

[c] $p<0.05$.

0.25 for the schizophrenic group and −0.14 for the group with affective psychosis. Step 5 in the regression equation indicated that the difference in these associations was significant (after intake level of functioning, demographic characteristics, and diagnosis were controlled). Similarly, interpretation of the significant interaction term for diagnosis by number of kin in the social network is aided by reference to the corresponding entries in table 2. There, number of kin is negatively associated with outcome for the schizophrenic group and positively associated with outcome for the affective group. The corresponding interaction term in step 5 of the regression equation indicated that this difference was significant. Overall, the addition of the social relationship variables and the interaction terms resulted in an increase of 15% in the explained variance of axis V ratings at 18 months (step 3 $R^2=0.39$, step 5 $R^2=0.54$).

DISCUSSION

We have compared subjects with first-episode schizophrenia to subjects with first-episode affective psychosis and normal subjects matched for age and sex. At entry to the study, three of six social relationship variables showed group differences, and nonsignificant trends ($p<0.10$) were apparent on two others. Schizophrenic subjects reported a smaller number of close and confiding relationships than did the other two groups, and they reported fewer friends in their social network than did the normal subjects.

Social relationships played an important role in the prediction of outcome: The number of nonkin in the social network made a positive contribution for subjects with schizophrenia and affective psychosis. Other social relationship variables worked in different ways for the two diagnostic groups: The number of kin in the network was negatively associated with outcome for schizophrenic subjects, but not for subjects with affective psychosis. Furthermore, greater availability of acquaintances was positively associated with outcome for schizophrenic subjects, but not for subjects with affective psychosis. Overall, social relationship variables played a more important role in the short-term course of schizophrenia than affective psychosis.

It is unlikely that attrition substantially affected the results. Since dropouts were, on the whole, older than those who remained in the study and came from somewhat lower socioeconomic backgrounds, the range of outcomes may have been slightly attenuated at the "good outcome" end. However, attrition rates were equal in the two diagnostic groups, and the characteristics of the dropouts were similar. Thus, it is unlikely that attrition accounted for the findings that social resources had a somewhat different effect in the two psychotic groups.

We have a limited understanding of how the loss of potential subjects before their entry into the study may have affected our results. The referred patients who refused to participate did not differ from participants in age or sex. However, ethical guidelines prohibited our gathering any other information. Whether because of ethical constraints or other reasons, the effect of this "pre-inclusion attrition" has not been addressed in the literature: Of the 30–35 studies of schizophrenia outcome, none report comparisons of participating subjects and subjects who met inclusion and exclusion criteria but who did not participate.

The group differences at intake are open to various interpretations. First, it is possible that, before becoming ill, schizophrenic subjects and persons with affective psychosis are less socially adept than normal individuals. However, it is difficult to separate premorbid personality from illness per se; thus, a second interpretation is that the small social network of schizophrenic subjects may be a symptom of illness rather than a measure of social skill. A third explanation would assign etiological significance to social relationships: A lack of resources or support may precipitate a psychotic episode.

Regarding the prediction of functioning at 18 months, we may have failed to control for some important third variable that accounts for the relationship between our predictors and outcome. For example, it may be true only for schizophrenic subjects with higher levels of social resources that much of their subsequent employment is arranged by friends. People with small social networks may be worse off because they avoid all social situations, as well as because of their lack of "connections."

Two other competing hypotheses derive from the fact that data on social resources and perceived social support were based on the patients' own perceptions. The negative association between kin in the social network and outcome may reflect an inability of schizophrenic subjects to tolerate intimate relationships and close contact. Thus, the negative association may arise because, compared to relationships with friends, relationships with family usually imply close physical proximity. One can get away from friends, but it is more difficult to escape family, particularly if they live under the same roof. Alternatively, the patients' self-report could be a reflection of critical, hostile, or overinvolved relatives. If so, our subjects may have been experiencing the negative effect of the "expressed emotion" phenomenon, which has, in turn, been related to poor outcome (36, 37).

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Suicidality, Depression, and Substance Abuse in Adolescence

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The authors assessed the occurrence of suicidal ideation, suicide attempts, major depression, and substance abuse in a sample of 424 apparently healthy college students 16–19 years old. Major depression and substance abuse were independent and interactive risk factors for suicidal ideation and for suicide attempts; substance abuse had a particularly deleterious effect on men. A prolonged desire to be dead was a more specific risk factor for a suicide attempt than was a thought of suicide. The authors conclude that suicidal ideation in the presence of major depression and/or substance abuse in older adolescents should call forth greater concern for lethality.

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We conducted a study to assess both the independent and interactive effects of major depression and substance abuse on suicidal ideation and suicidal behavior in adolescence. In addition, we examined the impact of three types of suicidal ideation on suicide attempts. Efforts to delineate high-risk adolescents are given urgency by the increase in the rate of suicide among 15–19-year-olds from 5.2 per 100,000 in 1970 to 9.0 per 100,000 in 1984 (1). Both major depression (2) and substance abuse (3) have been implicated as risk factors for adolescent suicide, but the clinical importance of suicidal ideation, a known risk factor for suicide in adults (4), has not been established among adolescents. The interaction among major depression, substance abuse, suicidal ideation, and suicidal attempts is unknown.

There are two methodological problems in determining the independent roles of these risk factors. First, major depression and substance abuse frequently coexist (5), making it difficult to assess which is primary, since each has been implicated as the cause of the other. Second, previously studied subjects have been drawn from groups of psychiatrically treated patients, raising the possibility of selection bias. Patients in treatment are more likely to have more than one disorder than those not in treatment. Therefore, the coexistence of disorders in such patients may inflate their apparent association compared with their potential independence as risk factors in affected persons not in treatment (6). As a result, the interconnections of major depression, substance abuse, suicidal ideation, and suicide attempts cannot be quantified in clinical samples, since the occurrence of these features together among psychiatric patients makes their disentanglement nearly impossible.

Until recently, studies involving psychiatric assessments of apparently healthy adolescents and that were both sufficiently detailed and consisted of large enough samples to be informative were too expensive to undertake. However, the introduction of the Diagnostic Interview Schedule (DIS) (7), a diagnostic instrument linked to the *DSM-III* classification of psychiatric illness that can be administered by trained lay interviewers, has opened new opportunities to ascertain histories of major depression, substance abuse, three forms of suicidal ideation, and suicide attempts in large groups of adolescents.

METHOD

The study sample consisted of 424 students (271 women and 153 men) attending two Boston area colleges: one a coeducational institution, the other an all-women's college. Nearly all subjects—398 (94%)—were either 18 or 19 years old; 305 (72%) came from the two highest social classes as defined by the Hollingshead index of paternal education. The sample was predominantly white; only 25 (6%) of the students were non-Caucasian (two of these were Asian).

Students were initially contacted by a letter describing the purpose of the study and what participation would entail and inviting their response on an enclosed self-addressed postcard. The study protocol, the method of contacting students, and informed consent procedures were approved by the Institutional Review Board of the Harvard School of Public Health and by the appropriate authorities at the two colleges.

The study sample of 424 students who agreed to participate represents 42% of the 1,018 eligible students asked to participate; 105 students refused and 489 did not respond. The students who refused were not contacted further, but the nonresponders were sent

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another letter at the end of the study asking if they would indicate the reasons for their nonresponse and if they would complete an enclosed 20-item self-report. The enclosed instrument was the Center for Epidemiologic Studies Depression Scale (CES-D Scale) (8), a validated screening instrument for depression. Fifty-six of the original nonresponders complied with these requests. The most common reasons for nonresponse were competing academic schedules, "forgetting to answer," or loss of the return postcard. The CES-D Scale scores of the 56 originally nonresponding students were compared with those of the 424 study participants and were found to reflect a slightly greater intensity of depressive symptoms, suggesting that depressive feelings may have influenced nonresponse.

Data for the study were obtained by using the DIS, a structured, standardized interview developed for epidemiologic purposes and previously used in the Epidemiologic Catchment Area Project (9) involving 20,000 subjects. Previous tests of reliability of the DIS based on the diagnostic agreement of psychiatrists and lay interviewers using it had resulted in the kappa value of 0.69 (7). The validity of the DIS has been assessed by the concordance of diagnoses generated by the DIS and those resulting from psychiatric interview. Concordance rates ranged from 0.79 to 0.96 depending on specific diagnoses, indicating the diagnostic validity of the DIS (10).

Before any data were collected, all interviewers received 10 hours of classroom training and 10 hours of field experience under the tutelage of an experienced DIS interviewer who had been trained by the developers of the instrument. The classroom training included discussion of the history, structure, and purpose of the DIS as well as familiarization with the flow chart, the probe, and the recording systems. The classroom training was followed by field experience in interviewing mental patients and observing others doing interviews. Videotaped interviews were used early in training and again at the end to provide opportunities for group scoring and discussion. We did not formally evaluate interrater reliability. However, the agreement on the scoring of the videotaped interview at the end of training was nearly perfect.

Data on the various gradations of suicidal thoughts and behavior were obtained by using four questions on the DIS that elicited a yes or no response. Three of these questions concerned suicidal ideations: Has there ever been a period of 2 weeks or more when you thought a lot about death—either your own, someone else's, or death in general? Has there ever been a period of 2 weeks or more when you felt you wanted to die? and Have you ever felt so low you thought of committing suicide? The fourth concerned suicidal behavior: Have you ever attempted suicide?

Data collected by using the DIS were entered directly into a computer and checked for accuracy by reentering. A specifically designed SAS program was used to determine the presence or absence of major depression and substance abuse for each subject.

Only subjects who met definite diagnostic criteria were considered positive for major depression or substance abuse. Major depression was determined by the coexistence of dysphoria lasting 2 weeks or more with at least four out of eight possible neurovegetative symptoms. Substance abuse, defined as either alcohol abuse or drug abuse or both together, was deemed present if the subject met *DSM-III* criteria for either of these two conditions.

The magnitude of the associations of the four gradations of suicidal thoughts or behavior with major depression and with substance abuse, separately, was estimated by computing the odds ratios and their 95% confidence intervals. Since a previous investigation had shown that major depression and substance abuse in this sample were associated with one another (5), stratification was used to control the effects of each of these two conditions in estimating the unconfounded associations with the four levels of suicidal ideation or behavior. The Mantel-Haenszel summary odds ratio was computed as the measure of unconfounded association (11).

RESULTS

The analyses of the data were designed to elucidate the following questions: Did the three queries on suicidal ideation constitute a gradation in intensity reflected by different probabilities of a suicide attempt? To what extent was suicidal ideation or behavior influenced by the presence of major depression? How was suicidal ideation or behavior influenced by the presence of substance abuse? Was there a gender difference in either the frequency or intensity of suicidal ideation or behavior?

Gradation of Suicidal Ideation or Behavior

There was a wide range in the rate of positive responses to the four questions. Forty-one percent (N=175) of the students admitted to having ruminated about death in general, 27% (N=115) reported having had suicidal thoughts, 9% (N=40) said that for at least 2 weeks they had experienced a desire to be dead, and 3.5% (N=15) stated that they had attempted suicide. The diversity in the percents of positive responses suggests a possible hierarchy of risk according to which general rumination about death would be the least specific risk factor for a suicide attempt and the desire to be dead the most proximal risk factor. The hypothesis of a gradient of risk was confirmed. Only 5% (N=9) of the 175 students who said that they had had thoughts about death in general were suicide attempters. However, 13% (N=15) of the 115 students who said that they had had suicidal thoughts and 25% (N=10) of the 40 students who said they had experienced a desire to be dead had attempted suicide. These data indicate that in this group of students a prolonged desire to be dead rather than thoughts of sui-

TABLE 1. Major Depression and Substance Abuse Among 424 Adolescent College Students

	Men (N=153)		Women (N=271)		Total (N=424)	
Diagnosis	N	%	N	%	N	%
Major depression plus substance abuse	2	1.3	6	2.2	8	1.9
Major depression without substance abuse	6	3.9	22	8.1	28	6.6
Substance abuse without major depression	15	9.8	17	6.3	32	7.5
No major depression and no substance abuse	130	85.0	226	83.4	356	84.0

cide were the most potent predictors of an actual suicide attempt.

Suicidal Ideation and Major Depression

The relationship between suicidal ideation and major depression is so widely accepted that further documentation seems hardly necessary. However, this well-established association has been observed primarily in clinical settings where the coexistence of suicidal ideation and major depression may, in part, result from selection bias. A nonpsychiatric college sample presents a unique opportunity to examine the relationship between various aspects of suicidal thoughts and major depression in the older adolescent.

In essentially all published studies, major depression has been found to be more common among women. The association between major depression and substance abuse is not so clear, although strong correlations have been shown between alcohol abuse and major depression, especially among men. Because of the potential confounding of major depression, substance abuse, and gender, all analyses have been controlled for these variables. Table 1 gives the distribution of major depression and substance abuse for our male and female subjects.

The associations between suicidal ideation or behavior and major depression are presented in table 2 by the odds ratios. An odds ratio of 1 indicates no association, whereas odds ratios larger than 1 indicate inverse associations. The greater the departure of the odds ratio from 1, the stronger the association. The crude odds ratios as well as the odds ratios adjusted for substance abuse are presented. Finally, the etiological fraction (12), which is the estimated proportion of suicidal ideation or behavior that can be attributed to major depression, is presented for each type of suicidal manifestation.

The data in table 2 show that every category of suicidal ideation was strongly associated with major depression, with odds ratios ranging from 6 to 22. When these odds ratios were adjusted for substance abuse, they were somewhat smaller, indicating that substance abuse was a confounder in that it not only was associated with major depression but also was an independent risk factor for suicidal ideation. The association of depression with all categories of suicidal ideation and behavior was statistically significant ($p<0.01$) for both crude and adjusted odds ratios. The greatest difference between the crude and adjusted odds ratios was seen in the association between major depression and suicide attempts. This suggests that substance abuse had a sizable independent impact on this extreme behavior. The proportion of suicidal ideation or behavior potentially attributable to major depression (the etiological fraction) ranged from a low of 12% for thoughts of death to a high of 48% for suicide attempts. The high etiological fraction for desire to be dead (45%) underscored its apparent close proximity to suicide attempts and reinforced the importance of major depression as a factor in these two more severe indications of suicidality.

The magnitude of the associations between major depression and the four categories of suicidal ideation or behavior should be tempered with the understanding that suicidality, as reflected in these four suicide items, was, in itself, one of the eight criteria considered in reaching the diagnostic threshold for major depression. We risk, then, somewhat overstating the association between major depression and suicidal behavior.

Suicidal Ideation and Substance Abuse

Table 3 shows the association between the four categories of suicidal ideation or behavior and substance abuse. The associations are measured both by the crude odds ratios and by the odds ratios adjusted for major depression. Overall, students with a diagnosis of substance abuse had a 2.1–3.7 times higher risk of suicidal ideation or behavior than did students without this diagnosis. When the associations were corrected to account for major depression, the odds ratios were still elevated but diminished. With the exception of thoughts of suicide ($p<0.05$), the associations were no longer statistically significant. The etiological fractions for substance abuse were smaller than those found for major depression but still accounted for a considerable proportion of suicidal ideation. This was particularly evident for suicide attempts and for the desire to be dead, in which an estimated 14.5% and 14% of these behaviors or thoughts were attributable to substance abuse.

Gender and Suicidal Ideation

In the field of suicide studies, paradoxical gender differences are well established. Among completed suicides, men outnumber women about 4 to 1. Conversely, among suicide attempters the ratio is inverted: women outnumber men about 3.5 to 1. Little is known, however, of the gender differences regarding suicidal thoughts in any group and especially among adolescents. Table 4 presents the rates of suicidal ideation or behavior for male and female students within each cate-

TABLE 2. Association Between Suicidal Ideation or Behavior and Diagnosis of Major Depression Among 424 Adolescent College Students

	Answer to Question on Suicidal Ideation or Behavior							
Item	Yes	No	Total[a]	Crude Odds Ratio	95% Confidence Interval	Adjusted Odds Ratio[b]	95% Confidence Interval	Etiological Fraction (%)
Thoughts of death	175	219	394	6.2	2.7–14.1	5.7	2.6–12.6	12.3
Students with diagnosis	26	6	32					
Students without diagnosis	149	213	362					
Thoughts of suicide	115	305	420	22.1	10.5–46.7	19.2	9.2–40.3	25.0
Students with diagnosis	31	5	36					
Students without diagnosis	84	300	384					
Desire to be dead	40	305	422	19.4	10.3–36.3	18.4	9.4–36.0	44.9
Students with diagnosis	19	17	36					
Students without diagnosis	21	365	386					
Suicide attempt	15	404	419	15.6	6.7–36.6	11.8	4.9–27.9	48.0
Students with diagnosis	8	28	36					
Students without diagnosis	7	376	383					

[a] Totals do not equal 424 due to missing data.
[b] Adjusted for substance abuse.

TABLE 3. Association Between Suicidal Ideation or Behavior and Diagnosis of Substance Abuse Among 424 Adolescent College Students

	Answer to Question on Suicidal Ideation or Behavior							
Item	Yes	No	Total[a]	Crude Odds Ratio	95% Confidence Interval	Adjusted Odds Ratio[b]	95% Confidence Interval	Etiological Fraction (%)
Thoughts of death	175	219	394	2.1	1.1–4.2	1.7	0.9–3.5	2.5
Students with diagnosis	22	14	36					
Students without diagnosis	153	205	358					
Thoughts of suicide	115	305	420	3.4	1.7–6.9	2.8	1.4–5.5	11.7
Students with diagnosis	21	19	40					
Students without diagnosis	94	286	380					
Desire to be dead	40	382	422	3.3	0.9–12.4	2.7	0.9–8.3	14.0
Students with diagnosis	9	31	40					
Students without diagnosis	31	351	382					
Suicide attempt	15	404	419	3.7	1.2–11.4	2.2	0.8–6.1	14.5
Students with diagnosis	4	36	40					
Students without diagnosis	11	368	379					

[a] Totals do not equal 424 due to missing data.
[b] Adjusted for major depression.

gory of suicidal thought or behavior. The percentages shown represent affirmative responses to the questions. The rates of the various forms of suicidal ideation are given separately for students with and without major depression or substance abuse.

In the absence of major depression and substance abuse, the frequency of suicidal ideation or behavior for both sexes was very similar. When major depression was present, the rate of suicidal ideation or behavior was markedly but equally higher for both men and women. For two of the four questions, women with major depression showed a higher rate than depressed men; for the other two questions, the reverse was true.

In contrast, the presence of substance abuse appeared to result in a dramatically higher rate of suicidal ideation for men over that of women. This was evident even when the baseline rate for women was higher than that of men. The higher rate of suicidal ideation or behavior among substance-abusing men was especially evident with regard to suicide attempts and desire to be dead, the same two categories that consistently appeared to be most specific of severity. Among women, the impact of substance abuse on suicidal ideation was not nearly so dramatic as it was for men, and it was considerably less than the impact of major depression.

DISCUSSION

The data from this study indicate a high rate of suicidal thoughts even in subjects who can be considered well functioning by virtue of their attendance at competitive colleges. That more than a quarter of the surveyed students had experienced suicidal thoughts at one time or another in their lives underscores the pervasiveness of such ideation but also highlights the lack of specificity of such thoughts as predictors of more serious behavior. It is likely that despite their high prevalence, thoughts of suicide are transitory. Their brief duration at any one time may make them partic-

TABLE 4. Suicidal Ideation or Behavior Reported by 424 Male and Female Adolescent College Students With and Without Major Depression or Substance Abuse

	Men			Women		
		With Suicidal Ideation or Behavior			With Suicidal Ideation or Behavior	
Suicidal Ideation or Behavior	Total	N	%	Total	N	%
Thoughts of death						
Major depression	8	7	87.5	28	22	78.6
No major depression	145	58	40.0	243	101	41.6
Substance abuse	17	12	70.6	23	12	52.2
No substance abuse	136	54	39.7	248	111	44.8
Thoughts of suicide						
Major depression	8	6	75.0	28	25	89.3
No major depression	145	30	20.7	243	54	22.2
Substance abuse	17	11	64.7	23	10	43.5
No substance abuse	136	25	18.4	248	70	28.2
Desire to be dead						
Major depression	8	3	37.5	28	16	57.1
No major depression	145	9	6.2	243	12	4.9
Substance abuse	17	12	70.6	23	6	26.1
No substance abuse	136	8	5.9	248	22	8.9
Suicide attempt						
Major depression	8	2	25.0	28	6	21.4
No major depression	145	0	0.0	243	6	2.5
Substance abuse	17	2	11.8	23	2	8.7
No substance abuse	136	0	0.0	248	10	4.0

ularly responsive to the social inhibitions that intervene between thought and action. These inhibiting factors are complex and include social sanctions against suicide; family, peer group, religious, and cultural influences; fear of the consequences of a failed attempt; and other constraints on the impulsivity that may accompany suicidal thoughts. Reports of cluster suicides in some communities or a slight increase in adolescent suicides following television programs on the subject (13–15) suggest that social or environmental factors may act transiently to overcome an inherent resistance to self-destruction. However, the role of the media in this regard is unclear, since a replicative study produced negative results (16).

Although both general thoughts of death and specific suicidal thoughts had been experienced by a large percentage of the group studied, the desire to be dead and actual suicide attempts were far less frequent. Furthermore, both of these more severe indicators were especially influenced by the presence of major depression and substance abuse. The data from this study confirm that, even in an untreated sample, a history of major depression is a strong correlate of a suicide attempt for both men and women. However, it is important to note that about half of the students who admitted having made a suicide attempt did not meet diagnostic criteria for major depression at any time in their lives. This finding was unexpected in the light of the body of published literature reporting an association between suicidal ideation and depression. Consistent with our finding, however, is the work of Vandivort and Locke (17). In their community study of nearly 4,000 adults, more than half of the men and one-third of the women who admitted having suicidal thoughts scored negative for depression on the CES-D Scale. The concordance of our findings with those of Vandivort and Locke suggests that, in community samples, the association of suicidal thoughts and depression may be muted. The strong association found in psychiatric samples could be partly explained by Berkson's bias (6), a form of selection bias that occurs when samples are drawn from treatment settings. Berkson's bias results from the fact that persons who have two or more disorders are more likely to be hospitalized than those who have only one disorder. Thus, individuals who are suicidal but not depressed are not as likely to be found in clinical settings as persons with both suicidal ideation and depression. We do not dispute that there is a true and valid correlation between suicidal thoughts and major depression, but we suggest that the association is not so strong in community settings.

The presence of substance abuse also elevates the risk of suicidal ideation or behavior, with the greatest impact seen on the two more severe items—the desire to be dead and a suicide attempt.

Feelings of despair and hopelessness figure importantly in suicidality. Beck et al. (18, 19) found an association between feelings of hopelessness and subsequent suicide attempts among adults (18), and Carlson and Cantwell (20) reported similar findings among children and adolescents. The hopelessness that derives from social distress may seek relief in substance abuse; thus, substance abuse becomes a secondary barometer of a disturbed life situation. Further, insofar as substance abuse contributes to deteriorating psychosocial function (21), situational distress is increased. Some adolescents become aware of the destructive effects of drugs and alcohol and try to stop further use. These attempts at sustained abstinence are often unsuccessful, leading to hopelessness about breaking the cycle of social distress, substance abuse, and suicidality.

The spectrum of suicide attempts ranges from relatively trivial gestures to those self-destructive acts of high lethality which require emergency medical attention. Previous studies have indicated that medical seriousness is linked to expressed seriousness of the adolescent's intent to die (desire to be dead). Further, a history of substance abuse has been correlated with medical seriousness and lethality of suicide attempts (22). Our data reinforce these findings and suggest that efforts to stem the tide of teenage suicide should focus on these groups at highest risk of lethal outcome.

We believe that these data have clinical implications. Those who work with depressed adolescents should determine whether there is a history of drug and alcohol abuse or current use. Those who treat substance abusers should focus on concomitant signs and symptoms of major depression. Finally, clinicians should be aware that, in the presence of major depression and/or substance abuse, suicidal ideation, especially a prolonged desire to be dead and a history of past attempts, should call forth heightened concern about suicide risk and should suggest a more intensive level of treatment than would be called for in the absence of these reinforcing factors.

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Psychiatric Disorders in the First-Degree Relatives of Probands With Bulimia Nervosa

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Data from a family study of psychiatric disorders showed higher rates of major affective disorders, eating disorders, and alcoholism in first-degree relatives of 40 bulimic probands than in first-degree relatives of 24 control subjects. More importantly, the data showed higher rates of major affective disorders in relatives of bulimic probands who themselves had no history of major affective disorders than in relatives of control subjects. This significant finding indicates a familial relationship between bulimia nervosa and major affective disorders, which suggests the possibility of a common diathesis.

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Strategies for conducting genetic investigation of bulimia nervosa include adoption studies, twin studies, and family studies. To date, there have been no adoption studies and only two twin case reports of bulimia (1, 2). However, several family studies have been conducted. These studies have been used to test the relationship between bulimia nervosa and other psychiatric disorders (3–8). In addition to formal family studies, clinical studies have also reported family histories of psychiatric disorders. Several have found evidence for a higher rate of affective disorders, substance use disorders, and eating disorders in the relatives of bulimic subjects than in the relatives of control subjects (9–20).

Table 1 outlines the family studies of bulimia to date. Variance in the findings is most likely attributable to methodological limitations, including small sample size, different diagnostic criteria, family history method (i.e., few relatives directly interviewed), and lack of an appropriate control group.

This paper presents the results of a family study of bulimia nervosa conducted within the Intramural Research Program at the National Institute of Mental Health (NIMH). The purpose of this study, from a clinical perspective, was to test the hypothesis of coaggregation of other psychiatric disorders with bulimia nervosa. Coaggregation is the frequent occurrence of two or more diseases in the same family, suggesting the possibility of a common diathesis (21).

We have attempted to control for the limitations that may have contributed to the different results in previous studies (21). We completed the study after the availability of precise diagnostic criteria for bulimia nervosa (*DSM-III-R*); we included 40 probands from our inpatient and outpatient protocols; and we included 24 nonpsychiatrically ill normal probands as a control group for the purposes of comparison. Finally, we used the family study method rather than the family history method, whereby all available first-degree relatives were interviewed. The family history method, while an important assessment technique in genetic studies, has been shown to underestimate prevalences of psychiatric disorders in relatives (22–24).

METHOD

The methods of family study have been described elsewhere (24–27). The patients were female bulimic subjects admitted to the intramural program at NIMH and their relatives. The control probands were normal volunteers and their relatives who responded to an advertisement for an NIMH study that was placed in a local newspaper and in the normal volunteer office of the National Institutes of Health, Bethesda, Md. (27). *DSM-III-R* criteria were used for bulimia nervosa, and modified Research Diagnostic Criteria (RDC) (28, 29) were used for all other psychiatric disorders. All reported rates of affective illness in relatives are age adjusted, for reasons noted and described elsewhere (25, 30). Similarly, reported rates of eating disorders in relatives are age adjusted, whereas reported rates of alcoholism, drug abuse, and antisocial personality are not (persons under age 16 are not considered at risk).

The 40 unrelated, normal weight bulimic probands

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TABLE 1. Studies of Psychiatric Disorders in Adult First-Degree Relatives of Bulimic Probands and Control Subjects

	Probands		Control Subjects			Higher Prevalence of Psychiatric Disorders in Proband Relatives Than in Control Relatives		
			Type of Control					
Study[a]	N	Relatives Interviewed	Diagnosis	N	Relatives Interviewed	Affective Disorders	Substance Use Disorders	Eating Disorders
Hudson et al. (3), 1983[b]	55	<66	Schizophrenia	39	—	Yes	—	—
			Bipolar disorder	33	—	No	—	—
			Borderline personality	15	—	Yes	—	—
Stern et al. (4), 1984[c]	27	27	Normal	27	27	No	No	—
Blouin et al. (5), 1986[d]	41	0	Normal	37	0	No	No	No
Stern et al. (6), 1986[c]	27	27	Normal	61	61	—	No	—
Bulik (7), 1987[c]	35	0	Normal	35	0	Yes	Yes	—
Hudson et al. (8), 1987[b]	69	0	Normal	28	0	Yes	Yes	No
			Unipolar disorder	24	0	No	Yes	No

[a] The study by Hudson et al. used the chart review and family history method; all other studies used the family history method.
[b] Probands, control subjects, and relatives diagnosed with *DSM-III* criteria.
[c] Probands and control subjects diagnosed with *DSM-III* criteria; relatives diagnosed with Research Diagnostic Criteria (RDC) and Family History-RDC.
[d] Probands and control subjects diagnosed with *DSM-III* criteria; diagnostic criteria for relatives not specified.

all met *DSM-III-R* criteria for bulimia nervosa, and none had a past history of anorexia nervosa. Body weights used in criteria for diagnosing anorexia nervosa were expressed as percentage of population average weight, adjusted for sex, age, and height. Patients were excluded from the study if they had met criteria for other major psychiatric disorders within the past year, with the exception of bulimic patients with a concurrent mood disorder. Bulimic probands were also ruled out of the study if they had medical problems unrelated to the bulimia. The mean±SD age at onset of bulimia in these patients was 17.3±0.6 years (range=11–29). The mean age of the patients at interview was 25.6±0.7 years (range=19–40).

Twenty-three bulimic probands had a history of a major affective disorder (unipolar disorder, N=16; bipolar II disorder, N=5; schizoaffective disorder, N=2), and 12 had a history of a minor affective disorder (minor depression, N=3; cyclothymia, N=4; hyperthymia, N=2; depressive personality, N=3). Twenty-two bulimic probands had a history of substance abuse. None of the 24 unrelated, normal control probands had a history of diagnosable psychiatric disorders, on the basis of information gathered with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (31), medical records, and history provided by relatives during the course of the study.

There were 4.6±2.1 adult first-degree relatives per bulimic proband and 4.9±1.8 per control proband, so it appeared reasonable to follow the usual custom in family studies of analyzing data in terms of morbid risk and reported rates in all relatives in a category, rather than reporting morbid risk and reported rates per family in each category. Sixty-two percent (N=188) of 303 first-degree relatives of patients and control subjects were interviewed with a modified SADS-L (32), 33% (N=100) refused to participate, and 5% (N=15) were deceased at the time of the interview. With 2.8±1.8 (range=0–8) relatives interviewed per bulimic proband, in addition to the bulimic proband's interview, and 3.0±2.4 (range=0–10) relatives interviewed per control proband, in addition to the control proband's interview, the number of individuals who were interviewed was sufficient to provide reliable information on uninterviewed relatives (24).

RESULTS

Table 2 compares rates of illness in relatives of bulimic probands with and without a major affective disorder with rates of illness in normal control subjects. Relatives of bulimic probands had a significantly higher morbid risk than relatives of control subjects for major affective disorders (combined bipolar and unipolar disorders), bipolar disorder, and unipolar disorder. Relatives of bulimic probands with a major affective disorder had a significantly higher morbid risk than relatives of control subjects for combined bipolar and unipolar disorders, bipolar disorder alone, and unipolar disorder alone. The morbid risk of combined bipolar disorder and unipolar disorder and bipolar disorder alone was significantly higher in relatives of bulimic probands without a major affective disorder than in control subjects. However, the morbid risk of unipolar disorder was not significantly higher in relatives of bulimic probands without a major affective disorder than in control subjects (parenthetically, we note the small number of relatives studied in this group). When

TABLE 2. Morbid Risk of Major Affective Disorders and Eating Disorders in Adult First-Degree Relatives of Bulimic and Normal Control Subjects

			Morbid Risk in Relatives (%)					
Proband Group	Families	Relatives	Bipolar Disorder	Unipolar Disorder	Bipolar and Unipolar Disorder	Bulimia Nervosa	Anorexia Nervosa	All Eating Disorders
Bulimia with major affective disorders	23	100	5.3[a]	29.5[b,c]	35.2[b,c]	10.4[a]	3.1	13.5[a]
Bulimia without major affective disorders	17	85	6.6[b]	12.5	19.1[a]	8.6	1.2	9.8
Total bulimia	40	185	5.9[a]	22.0[b]	27.9[d]	9.6[a]	2.2	11.8[a]
Control	24	118	0.0	8.3	8.8	3.5	0.0	3.5

[a] Significantly higher risk than for control group ($p<0.05$; comparisons made with chi-square 2×2 contingency tables).
[b] Significantly higher risk than for control group ($p<0.01$).
[c] Significantly higher risk than for bulimic group without major affective disorders ($p<0.01$).
[d] Significantly higher risk than for control group ($p<0.001$).

TABLE 3. Reported Rates of Substance Use Disorders and Antisocial Personality in Adult First-Degree Relatives of Bulimic and Normal Control Subjects

			Relatives					
			Alcoholism		Drug Abuse		Antisocial Personality	
Proband Group	Families	Relatives	N	%	N	%	N	%
Bulimia with major affective disorders	23	100	33	33.0[a]	15	15.0[b]	6	6.0[b]
Bulimia without major affective disorders	17	85	19	21.9	7	8.2	3	3.5
Total bulimia	40	185	51	27.6[a]	22	11.9	9	4.9[a]
Control	24	118	16	13.6	7	5.9	1	0.8

[a] Significantly higher risk than for control group ($p<0.01$; comparisons made with chi-square 2×2 contingency tables).
[b] Significantly higher risk than for control group ($p<0.05$).

we compared the bulimia group with major affective disorders to the bulimia group without major affective disorders, we found that the former group had a significantly higher rate of combined bipolar disorder and unipolar disorder and unipolar disorder alone, but not bipolar disorder alone.

Table 2 also shows that the relatives' morbid risk of total eating disorders was significantly higher in the bulimic group than in the control group. We found that the morbid risk of bulimia in relatives was significantly higher in the bulimic than in the control group and that relatives of bulimic probands were three times as likely to be bulimic as control relatives were. However, the risk of anorexia nervosa was not significantly higher in relatives of bulimic probands than in relatives of control subjects, but because anorexia nervosa is less common, a small difference might have been missed.

Table 3 reports rates of alcoholism, drug abuse, and antisocial personality in adult first-degree relatives of bulimic and control subjects. The reported rates of alcoholism were significantly higher among relatives of bulimic probands than relatives of control subjects. Drug abuse rates in relatives of bulimic probands only reached significance when we compared bulimic probands with major affective disorders to control subjects. The reported rates of antisocial personality almost reached significance in relatives of bulimic probands when compared to those of control subjects.

DISCUSSION

This study points to the role of comorbidity of psychiatric disorders in the bulimic probands. Twenty-three probands (58%) met criteria for major affective disorders, and 22 (55%) met criteria for substance use disorders. While we only examined antisocial personality disorder, researchers are also becoming more aware of the need to look systematically at the relationship between bulimia nervosa and the personality disorders.

This study also supports the hypothesis of coaggregation of other psychiatric disorders with bulimia. Our results indicate significantly higher rates of major affective disorders, eating disorders, and alcoholism in the families of bulimic probands than of control subjects.

More importantly, the data showed higher rates of major affective disorders (combined bipolar disorder and unipolar disorder) and of bipolar disorder alone in relatives of bulimic probands who themselves had no history of major affective disorders than in relatives of control subjects. This significant finding indicates a familial relationship between bulimia and major affective disorders, which suggests the possibility of a common diathesis.

From this study, we conclude that bulimia nervosa is clearly associated with significant psychopathology in patients and their relatives. This information should be considered when conducting research in areas such as etiology, treatment, and course of illness.

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Dementia With Coexistent Major Depression

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Eleven percent (N=25) of 232 dementia patients seen in an active geropsychiatry service also met criteria for major depression. Ten patients with dementia/depression were prospectively compared with 10 nondepressed demented and 33 nondemented depressed patients on pretreatment and posttreatment ratings of depression and cognition/memory. Seventy percent (N=7) of the dementia/depression group and 73% (N=24) of the depression-only group responded to antidepressant therapy. Signs and symptoms of depression complicating dementia were similar to depressive phenomena in the depression-only group. Depression with dementia appeared to lower performance on cognitive tests. Following treatment, although cognitive impairment remained in the demented range, test performance improved.

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Intermittent depressive phenomena are frequently part of the dementia syndrome. Such depressive features have been reported to occur in as many as 50% of dementia patients (1, 2). Less commonly encountered in dementia is a sustained depressive syndrome (3, 4). When this occurs, the cognitive impairment that may be associated with depression (5, 6), especially in the elderly (7), could exacerbate the severity of the underlying dementia. Successful somatic treatment of depression should improve this reversible component of cognitive dysfunction (5). Although numerous studies have examined depressive features in dementia (8–16), only a few have focused on a superimposed major depressive episode and its treatment (17–20).

The purpose of this study was to address the following questions. 1) How common is a concurrent major depressive episode in dementia? 2) Is this syndrome phenomenologically distinct? 3) Does depression interact with dementia to have an effect on cognitive performance? 4) What are the response rates to somatic treatment?

METHOD

Three groups of elderly psychiatric patients were studied. Group 1 (depression only) consisted of 33 depressed inpatients (25 female and eight male; mean ±SD age=76.45±5.06 years) who met the *DSM-III* criteria for a major depressive episode, unipolar type. The patients had no other *DSM-III* axis I disorder. Group 2 (dementia/depression) contained 10 patients (seven female and three male; mean±SD age=83.40 ±4.40 years) who met the *DSM-III* criteria for both dementia and a major depressive episode. Before the onset of depressive signs and symptoms, they had had definite diagnoses of *DSM-III* dementia for at least 1 year (i.e., there were no patients with dementia syndrome of depression or depressive pseudodementia). These patients had no previous history of affective illness. Group 3 (dementia only) consisted of 10 patients (six female and four male; mean±SD age=77.60± 6.93 years) who had met the *DSM-III* criteria for dementia for at least 1 year and had no history of affective illness. All patients were inpatients on the Mount Sinai Hospital geriatric psychiatry inpatient unit, except three patients from group 3, who were seen in the Mount Sinai geropsychiatry outpatient clinics.

Reversible causes of dementia and/or factors contributing to it were ruled out by means of a standard dementia work-up. This included psychiatric, neurological, and medical examinations, CBC, a chemistry profile, determination of vitamin B_{12}/folate levels, thyroid function tests, a serological test for syphilis, urinalysis, chest X-ray, ECG, EEG, and a brain CT scan and/or magnetic resonance imaging. All dementia patients (groups 2 and 3) had diagnoses of either Alzheimer's disease or multi-infarct dementia. Alzheimer patients met the *DSM-III* criteria for primary degenerative dementia and the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (21) for probable Alzheimer's disease. Patients with multi-infarct dementia met the *DSM-III* cri-

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teria for this diagnosis and also had evidence on CT scan of brain infarct. There were six patients with Alzheimer's disease and four patients with multi-infarct dementia in group 2 and five patients with each diagnosis in group 3. All patients had been free of psychoactive drugs for at least 1 week and had no acute medical illnesses or exacerbation of any chronic medical conditions.

Following a suitable time period to allow for acclimatization to the inpatient unit, we evaluated patients prospectively on a variety of standardized neuropsychiatric rating scales. Cognitive status was assessed at admission and discharge by psychiatric residents assigned to the geropsychiatry service. The residents were blind to the hypotheses being tested and were trained in the use of the scales. The Mini-Mental State examination (22) was given to all groups (range of possible scores=0–30). In addition, demented patients (groups 2 and 3) were evaluated with the Memory and Information Test (23) (range of possible scores=0–20) and the Dementia Rating Scale (24) (range of possible scores=0–17). Dementia ratings were part of the routine comprehensive work-up.

All patients consented to be interviewed for depression assessments. An experienced geriatric psychiatrist (B.S.G.) and psychologist (E.K-G.) made simultaneous depression ratings without knowledge of the dementia ratings. The interrater reliability for the depression ratings, as determined by the intraclass correlation coefficient (25), was 0.90 ($p<0.001$). The degree of depression was assessed on admission and at discharge by means of the Hamilton Rating Scale for Depression (26) and the Clinical Global Impression (CGI) (27). The phenomenology of depressive characteristics in all groups was examined. A comprehensive inventory of depressive symptoms was established by incorporating items related to depression from two semistructured psychiatric interview schedules: the Schedule for Affective Disorders and Schizophrenia (SADS) (28) and the Present State Examination (PSE) (29). A small number of additional depressive features, not specifically categorized in either the SADS or the PSE, were included for completeness. All items were rated on a 3- or 4-point scoring system. (A copy of this inventory of depressive symptoms is available from the first author on request.) A list of the items with their respective SADS or PSE numbers is presented in appendix 1.

All group 1 and group 2 patients were treated naturalistically with conventional somatic antidepressant therapy (drugs or ECT). Four of the 10 group 3 patients (all hospitalized) required low doses of sedative medication. Responsiveness to treatment was defined as a decrement of 10 or more points on the Hamilton depression scale and of 2 or more points on the CGI.

To ascertain the frequency of coexistent dementia and major depression, records of all dementia patients seen by the Mount Sinai geropsychiatry service (inpatient and outpatient) over a 2½-year period (January 1986 to June 1988) (N=232) were reviewed for diagnoses of concomitant *DSM-III* major depressive episodes. All patients met the *DSM-III* criteria for dementia. This retrospective approach allowed consistent *DSM-III* categorization of patients with primary degenerative dementia (Alzheimer's disease), multi-infarct dementia, and other dementias. Because operationalized criteria for mixed dementia (i.e., presumed multi-infarct dementia and Alzheimer's disease) could not be reliably applied during this review process, patients with suspected mixed dementia, nearly all of whom had CT evidence of infarct, were included in the multi-infarct dementia group.

To determine whether unique and clinically relevant characteristics identified the dementia/depression cohort, we analyzed differences between groups on the various rating scales at admission and at discharge by means of analysis of variance. Since significant differences between groups were demonstrated for age ($F=6.31$, $df=2, 50$, $p<0.04$), we did analyses of covariance when appropriate. Paired t tests were used to analyze whether there were significant differences within groups on the various rating scales from admission to discharge. Two-tailed tests were used for all levels of significance.

RESULTS

The overall frequency of major depression complicating preexisting dementia was 11% (25 of 232 patients). The mean±SD age of the entire sample was 75.27±9.39 years, with a range of 51 to 97. There were 65 men and 167 women. The prevalence of depression in subgroups of demented patients was also examined; 8% (13 of 157) of the patients with Alzheimer's disease, 20% (11 of 54) of those with multi-infarct dementia, and 5% (one of 21) with "other" dementia were depressed.

Mean scores on the SADS-PSE depression items that were significantly different between the three small groups we studied are presented in table 1. Dementia/depression patients (group 2) were distinguished from the other two groups only by symptoms of self-pity and rejection sensitivity. However, dementia/depression and depression-only patients shared many classical depressive features that the dementia-only patients did not. These included overt indices of dysphoria (depressed mood, depressed appearance), vegetative symptoms (poor appetite, loss of weight, anergia), markers of intrapsychic distress (helplessness, worrying, psychic anxiety), and negative symptoms (anhedonia, blunted affect, social withdrawal, lack of environmental reactivity). Depression-only patients manifested greater emptiness, sleeplessness, and systematization and mood congruency of delusions than the demented groups.

Patients' mean scores on the standardized rating scales at admission and at discharge are presented in table 2. On admission, ratings of depression severity (total Hamilton depression score and CGI) were similar in the depression-only and dementia/depression

TABLE 1. Significant Differences in Scores of Depressed and/or Demented Patients on an Inventory of Depressive Symptoms[a]

	Score							
	Depression Only (group 1) (N=33)		Dementia/ Depression (group 2) (N=10)		Dementia Only (group 3) (N=10)			
Symptom	Mean	SD	Mean	SD	Mean	SD	F (df=2, 50)	p
Depressed mood (subjective)[b]	1.64	0.81	1.50	0.71	0.50	0.53	10.10	0.0002
Worrying[c]	1.87	1.07	1.10	0.74	0.70	0.95	9.36	0.0004
Loss of interest[b]	1.53	0.81	1.30	1.05	0.50	0.71	5.05	0.01
Anhedonia[c]	1.61	0.84	0.90	0.57	0.00	0.00	23.30	<0.0001
Lack of environmental reactivity[b]	0.97	0.81	1.00	0.67	0.00	0.00	7.63	0.001
Anergia[b]	1.80	0.44	1.70	0.42	0.20	0.42	20.72	<0.0001
Emptiness, boredom[d]	1.06	0.84	0.57	0.79	0.22	0.53	3.97	0.03
Helplessness[b]	1.00	0.95	1.14	1.15	0.00	0.74	5.28	0.01
Psychic anxiety[b]	1.54	0.76	1.00	1.05	0.30	0.48	8.30	0.0008
Delayed sleep (initial insomnia)[d]	1.27	0.93	0.70	0.84	0.60	0.94	5.07	0.01
Early waking[d]	0.79	0.53	0.40	0.52	0.20	0.42	4.30	0.02
Poor appetite[b]	1.15	0.88	0.90	0.74	0.40	0.70	3.54	0.04
Loss of weight[b]	1.35	0.69	0.80	0.42	0.30	0.48	6.79	0.003
Indecisiveness[b]	1.02	0.84	1.00	0.67	0.20	0.42	3.81	0.03
Memory or orientation disturbance[e]	0.73	0.83	2.00	0.94	2.00	0.47	14.83	<0.0001
Social withdrawal[b]	1.50	0.75	1.30	1.05	0.50	0.71	4.22	0.01
Rejection sensitivity[f]	0.13	0.79	0.44	0.70	0.00	0.95	6.01	0.005
Blunted affect[b]	1.00	0.88	1.20	0.79	0.30	0.67	4.23	0.02
Self-pity[f]	0.54	0.88	1.20	0.74	0.30	0.48	4.71	0.01
Depressed appearance[b]	1.54	0.84	1.60	0.84	0.40	0.52	10.27	0.0002
Mood congruency of delusions[d]	1.43	0.80	0.40	0.84	0.00	0.00	8.19	0.002
Systematization of delusions[d]	1.14	0.82	0.30	0.67	0.00	0.00	7.21	0.002

[a] SADS-PSE ratings (see appendix 1).

[b] Groups 1 and 2 significantly greater than group 3.

[c] Group 1 significantly greater than groups 2 and 3; group 2 significantly greater than group 3.

[d] Group 1 significantly greater than groups 2 and 3.

[e] Groups 2 and 3 significantly greater than group 1.

[f] Group 2 significantly greater than groups 1 and 3.

groups. Both were significantly more depressed than the dementia-only patients. However, discharge depression scores were equivalent in all groups. Within groups, degree of depression was significantly reduced from admission to discharge in both of the depressed samples but not in the dementia-only group.

Level of cognitive function at admission and discharge, as assessed by the Mini-Mental State examination, was significantly better in the depression-only group than in the other groups. Dementia/depression patients had consistently worse performance at admission on all three cognitive measures than dementia-only patients. However, at discharge, differences in cognitive ratings between the two dementia groups were no longer present, suggesting a similar degree of underlying impairment.

Mini-Mental State scores significantly improved from admission to discharge in the depression-only group. Similarly, in the dementia/depression group, scores on all cognitive tests improved following treatment at either a significant (Dementia Rating Scale) or nearly significant (Mini-Mental State, Memory and Information Test) level. Within the dementia-only group, changes in cognitive scores from admission to discharge were inconsistent between tests and did not approach statistical significance.

Seventy percent (N=7) of the dementia/depression group and 73% (N=24) of the depression-only group responded (according to the criteria outlined) to somatic antidepressant treatment. Choice of therapy was based on medical status, clinical symptoms, and preadmission treatment history. Within the dementia/depression group, all patients required sequential—at times, complicated—treatment trials (see table 3). Changes in treatment resulted from failure of a treatment and/or development of intolerable side effects. Because of the well-described acute cognitive effects of ECT, our treatment bias was to begin with medication, unless this was contraindicated. Of the 33 depression-only patients, 27% (N=9) received a tricyclic antidepressant alone, 12% (N=4) received a tricyclic and a neuroleptic, 6% (N=2) received a monoamine oxidase inhibitor alone, 27% (N=9) received unilateral ECT, and 18% (N=6) failed to respond to three to five unilateral treatments and received bilateral ECT. The three remaining patients were treated with lithium, alprazolam, and haloperidol, respectively. Dementia-only patients intermittently received various psychotropics for symptoms of agitation, anxiety, psychosis, and insomnia.

Hospital stays for active psychiatric assessment/treatment were significantly longer for the dementia/depression group (mean±SD=78.0±29.3 days) than for the depression-only group (45.0±26.9 days) and

TABLE 2. Rating Scale Scores of Depressed and/or Demented Patients at Hospital Admission and at Discharge

	Score[a]								
	Depression Only (group 1) (N=33)		Dementia/ Depression (group 2) (N=10)		Dementia Only (group 3) (N=10)				
Rating Scale	Mean	SD	Mean	SD	Mean	SD	F or t	df	p
Hamilton depression scale									
Admission	21.12	7.27	18.90	5.09	6.40	4.53	35.17	2, 50	<0.0001
Discharge	5.55[b]	5.03	4.90[c]	3.80	3.56[d]	0.69	0.59	2, 47	n.s.
Clinical Global Impression									
Admission	4.31	1.08	4.00	0.47	2.04	0.69	21.98	2, 50	<0.0001
Discharge	1.89[e]	0.96	1.80[f]	0.79	1.75	0.50	0.11	2, 47	n.s.
Mini-Mental State									
Admission	24.84	5.41	16.60	4.12	18.80	3.46	13.38	2, 49	<0.0001
Discharge	27.93[g]	1.94	18.70[h]	5.40	19.00	4.40	19.21	2, 46	<0.0001
Memory and Information Test									
Admission	—	—	3.30	2.63	6.90	3.00	10.64	17	<0.01
Discharge	—	—	7.14[i]	5.37	5.29	2.98	0.40	13	n.s.
Dementia Rating Scale									
Admission	—	—	9.70	2.16	6.14	1.86	8.67	17	<0.01
Discharge	—	—	5.86[j]	3.13	5.80	2.68	0.15	13	n.s.

[a] Lower scores on the Hamilton scale, the CGI, and the Dementia Rating Scale indicate better functioning; higher scores on the Mini-Mental State and the Memory and Information Test indicate better functioning.
[b] Group 1 admission score greater than discharge score (t=10.73, df=31, p<0.0001).
[c] Group 2 admission score greater than discharge score (t=6.21, df=8, p<0.0001).
[d] Group 3 admission score greater than discharge score (t=3.54, df=6, p<0.02).
[e] Group 1 admission score greater than discharge score (t=10.72, df=31, p<0.0001).
[f] Group 2 admission score greater than discharge score (t=7.57, df=8, p<0.0001).
[g] Group 1 admission score less than discharge score (t=3.55, df=30, p<0.01).
[h] Group 2 admission score less than discharge score (t=3.07, df=8, p=0.06).
[i] Group 2 admission score less than discharge score (t=2.20, df=8, p=0.07).
[j] Group 2 admission score greater than discharge score (t=2.90, df=6, p<0.03).

TABLE 3. Antidepressant Treatments of 10 Dementia/Depression Patients

Patient	Treatments[a]
1	Trazodone; six unilateral ECTs
2	Tranylcypromine; nortriptyline
3	Five unilateral ECTs; three bilateral ECTs
4	Desipramine; tranylcypromine; phenelzine
5	Fluphenazine; four unilateral ECTs; trazodone[b]
6	Tranylcypromine; eight unilateral ECTs
7	Tranylcypromine; methylphenidate; four unilateral ECTs; seven bilateral ECTs
8	Nortriptyline; nortriptyline plus lithium; nortriptyline plus methylphenidate; five unilateral ECTs; eight bilateral ECTs
9	Desipramine; nortriptyline plus haloperidol[b,c]
10	Maprotiline; tranylcypromine[b,c]

[a] Treatments represent *sequential* trials.
[b] Nonresponder.
[c] Refused ECT.

dementia-only group (44.5±16.6 days) (F=6.22, df=2, 47, p<0.004).

DISCUSSION

Eleven percent of the demented patients seen in our inpatient and outpatient geropsychiatry service had a superimposed major depressive episode. The reported prevalence of depression complicating preexisting dementia varies widely (3, 4, 10, 17–19, 30) and ranges from 0% (10) to 85% (30). These large fluctuations in rates of depression in dementia are no doubt partly a consequence of the differences across studies in the criteria for depression. Many descriptive studies merely reflect the presence of nonspecific depressive features, several of which overlap with core dementia symptoms (9, 13), rather than full depressive syndromes. Such phenomenological differences were conceptually delineated in a study done in the 1950s (3). The relatively more common "affective coloring" with only transient and fragmentary ("shallow and short-lived") depressive characteristics in demented individuals was contrasted with the infrequently encountered "sustained depressive symptom complex" that probably approximates today's "major depressive episode." The present study's 11% prevalence of *major* depression in dementia falls between the 2.7% rate in the early study (3) and the 25% syndromal rate in more recent reports (17, 18).

Another possible explanation for differences in prevalence rates between studies may be the inconsistent inclusion or exclusion of different types of dementia. For example, several investigators have noted the greater occurrence of depression in multi-infarct dementia patients than in Alzheimer's disease patients (3, 4, 11, 15). Our investigation similarly found a higher frequency of depression in patients with multi-infarct dementia (20%) than in patients with Alzheimer's disease (8%). These data support the association between cerebrovascular disease and affective vulnerability (31). Treatment-responsive (32, 33) poststroke depression may develop in 30%–60% of patients with cerebrovascular accidents (34–36). A recent estimate suggested that 53% of patients with cerebrovascular accidents will go on to develop multi-infarct dementia (37). Neurochemical mechanisms that involve the two major neurotransmitter systems linked to major depression have recently been implicated in depression complicating brain disease. Noradrenergic (31, 38) and serotonergic (39) effects of ischemic brain injury have been related to the pathogenesis and severity of poststroke depression. In patients with Alzheimer's disease, reduced noradrenergic and serotonergic function (40–48) has been hypothesized to underlie the development of depression (49, 50). Recently, greater locus ceruleus and substantia nigra neuronal degeneration has been reported in depressed than in nondepressed dementia patients (51).

For the most part, the clinical features of depression complicating dementia are similar to depressive phenomena occurring in elderly depressed patients. Our prestudy suspicion that demented patients, when depressed, might develop an unusual or unique symptom profile was not supported. Similar results were obtained in a study that compared phenomenological characteristics of patients with poststroke depression and age-matched patients with "functional depression" (52).

In nondemented patients, particularly the elderly, a major depressive episode may be associated with reversible cognitive impairment (5–7). In fact, for our elderly depression-only group, mean scores on the Mini-Mental State examination were significantly higher following treatment than at admission. In our patients with coexistent syndromes, depression appeared to interact with dementia to lower performance on cognitive tests. Performance, although remaining in the severely impaired range, improved following antidepressant treatment. A study that evaluated antidepressant treatment effects in eight patients with primary degenerative dementia with depressive features (20) reported no significant improvement on the Mini-Mental State or the Washington University Clinical Dementia Rating Scale, but a trend toward improvement as measured by the Blessed Dementia Rating Scale was demonstrated. Several anecdotal reports have also described concomitant improvements in mood and cognition following somatic antidepressant therapy in demented patients with superimposed depression (18, 53–55). The fact that cognitive improvements were not evidenced in our dementia-only group argues against the possible beneficial effects of hospitalization, participation in structured activities, discontinuation of centrally active medications, and patient/family engagement.

In this study the diagnosis of depression in dementia patients was validated by a treatment response rate (70%) that generally reflects outcomes of standardized treatment trials in late-life depression (56, 57) and that paralleled the rate of response in our depression-only group. Successful outcomes often depended on persistent and aggressive treatment approaches, including sequential trials of different antidepressants and ECT. Although initial treatment failures and intolerance of side effects were common, our results suggest that *syndromal* depression complicating dementia is a treatable condition. Standardized, double-blind, placebo-controlled studies of dementia patients with this syndrome are needed. This study did not address the effects of antidepressant treatment of subsyndromal depressive features in demented patients.

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APPENDIX 1. Inventory of Depressive Symptoms Largely Derived From the Schedule for Affective Disorders and Schizophrenia (SADS) and the Present State Examination (PSE)

1. Subjective feelings of depression based on verbal complaints (SADS item 234; PSE item 23)
2. Worrying, brooding, painful preoccupation, and inability to get mind off unpleasant thoughts (SADS 238; PSE 4)
3. Self-reproach, pathological guilt (*not* delusional) (SADS 240; PSE 33)
4. Self-depreciation; negative evaluation of self, including feelings of inadequacy, failure, worthlessness (SADS 242; PSE 29)
5. Discouragement, pessimism, hopelessness (SADS 244; PSE 24)
6. Loss of interest (SADS 326; PSE 22)
7. Anhedonia (loss of pleasure)
8. Loss of libido within present episode of illness (SADS 326; PSE 38)
9. Lack of environmental reactivity (SADS 350)
10. Subjective feeling of irritability, anger, annoyance, resentment (SADS 330; PSE 40)

11. Anergia (lack of energy, fatigue, tiredness, exhaustion) (SADS 315; PSE 6, 36)
12. Emptiness (depletion, boredom, meaninglessness, detachment)
13. Helplessness
14. Suicidal tendencies (SADS 246; PSE 25)
15. Somatic anxiety (SADS 263; PSE 11)
16. Psychic anxiety (SADS 265; PSE 10)
17. Muscular tension (SADS 263; PSE 7)
18. Tension pains (PSE 5)
19. Delayed sleep (SADS 272, 273; PSE 35)
20. Middle insomnia
21. Early waking (SADS 272, 275; PSE 37)
22. Hypersomnia (SADS 314)
23. Poor appetite (SADS 317; PSE 34)
24. Loss of weight during present episode (SADS 319; PSE 34)
25. Increase in appetite (SADS 320)
26. Weight gain from usual weight during present episode (SADS 321)
27. Constipation
28. Somatic gastrointestinal symptoms
29. Indecisiveness (SADS 324; PSE 19)
30. Subjectively inefficient thinking (SADS 325; PSE 19)
31. Poor concentration (SADS 325; PSE 20)
32. Memory or orientation disturbance (SADS 464; PSE 103)
33. Derealization (SADS 329; PSE 47)
34. Depersonalization (SADS 329; PSE 48)
35. Social withdrawal (SADS 328; PSE 28)
36. Hypochondriasis (SADS 322; PSE 9)
37. Diurnal mood variation, worse in the morning (SADS 351; PSE 27)
38. Diurnal mood variation, worse in the evening
39. Obsessions or compulsions (SADS 270; PSE 44, 45, 46)
40. Suspiciousness (SADS 418; PSE 31, 125)
41. Nondelusional ideas of reference (SADS 420; PSE 31, 32)
42. Leaden feeling or extreme body inertia
43. Rejection sensitivity
44. Overt expression of irritability, annoyance, anger (SADS 332; PSE 40, 124)
45. Agitation (SADS 334; PSE 8, 111)
46. Psychomotor retardation (SADS 342; PSE 110, 130, 133, 134)
47. Blunted affect (SADS 469; PSE 128)
48. Distractibility (SADS 470; PSE 114)
49. Self-pity (SADS 471)
50. Demandingness or dependency (SADS 472)
51. Depressed appearance (SADS 473; PSE 121)
52. Self-neglect (SADS 473; PSE 108)
53. Severity of delusions of any type (SADS 433; PSE 95)
54. Mood congruency of delusions (SADS 437; PSE "15G")
55. Multiple delusions (SADS 439)
56. Systematization of delusions (PSE 93)
57. Severity of hallucinations of any type (SADS 450; PSE 95)
58. Mood congruency of hallucinations (SADS 452, 457; PSE 61)

Response to Sodium Lactate Infusion in Alcoholics With Panic Attacks

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The authors studied the response to sodium lactate infusion of 12 alcoholics with a history of panic attacks, 10 alcoholics without a history of panic attacks, and 16 nonalcoholic patients with panic disorder. The rate of lactate-induced panic was significantly higher in alcoholics with panic attacks than in alcoholics without panic attacks. Alcoholics with panic attacks were similar to nonalcoholic patients with panic disorder in their response to lactate. These findings support the specificity of lactate-induced panic for panic states and suggest that panic attacks in alcoholics resemble those in nonalcoholics. Lactate infusion may prove useful in the diagnosis of panic disorder in alcoholics.

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The comorbidity of alcoholism and panic disorder has been demonstrated. In 1972, Quitkin et al. (1) identified alcohol and sedative abuse as complications of panic attacks. Alcohol problems have been reported in 28% of outpatients with panic disorder (2), and successful imipramine treatment of both panic disorder and coexisting alcoholism has been described in isolated case reports (1, 3). Panic disorder has been found in 1.2% to 21% of alcoholic inpatients (4–6), and the rate of agoraphobia in alcoholic inpatients has been reported to be from 12% to 41% (6–8).

The relationship of panic and anxiety disorders to alcoholism remains unclear. Most anxious alcoholics report that their anxiety symptoms and phobias predated the onset of their problem drinking (4–6). Phobic alcoholics studied by Stockwell et al. (9) reported that drinking helped them to face feared situations; in fact, many of them used alcohol deliberately for this purpose. Ethanol shows cross-tolerance with antianxiety agents such as benzodiazepines and barbiturates (10).

On the other hand, prolonged alcohol consumption may increase anxiety and phobias (9). Ethanol has a short half-life, and, like withdrawal from short-acting benzodiazepines, withdrawal from ethanol may produce rebound anxiety (11). Both anxiety and hyperventilation, which is often associated with panic (12), may be part of a prolonged, subacute alcohol withdrawal syndrome (13). Finally, the fact that symptoms of panic attacks resemble those of alcohol withdrawal makes diagnosis of panic attacks very difficult in chronic alcoholics and has led some investigators (14) to propose that panic attacks in chronic alcoholics often may be withdrawal symptoms.

Given the difficulty both in diagnosing panic attacks in alcoholics and in determining the causal relationship between alcoholism and panic, it would be useful to develop a diagnostic test for panic in alcoholics and to compare alcoholics with panic attacks and nonalcoholic patients with panic disorder using an independent biological measure.

Intravenous infusion of sodium lactate has been studied extensively as a possible biological marker for panic attacks. Lactate infusion provokes physiological and psychological symptoms of panic in patients with panic attacks at a significantly higher rate than in normal control subjects or patients with other psychiatric disorders without coexisting panic attacks (15–17). Although the mechanism of lactate-induced panic is as yet unknown, patients who experience typical panic attacks with lactate infusion have been reported to show greater blood flow to the right parahippocampal gyrus on positron emission tomography (PET) scans performed in the resting, nonpanic state (18), suggesting that lactate sensitivity may mark a subset of patients with panic attacks who have a distinctive biological vulnerability to panic.

Our aim in the study reported here was to determine whether response to lactate infusion differentiates alcoholics with and without carefully diagnosed, definite

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panic attacks. In addition, primary alcoholics with panic attacks were compared with patients with panic disorder without a history of alcoholism, with the hypothesis that these two groups would be similar in their sensitivity to lactate.

METHOD

The subjects were 16 nonalcoholic men with *DSM-III* panic disorder, 12 men with *DSM-III* alcohol dependence and a history of panic attacks as defined in *DSM-III,* and 10 men with *DSM-III* alcohol dependence without a history of panic attacks. All subjects provided written informed consent to their participation in the study as required by the University of Washington Institutional Review Board.

The 16 nonalcoholic patients with panic disorder were consecutive male outpatients who underwent lactate infusion before beginning psychopharmacology treatment studies. Two of these men had a past history of nonalcohol substance abuse; none had a history of agoraphobia. Psychiatric diagnoses were made by experienced psychiatrists using a semistructured interview based on *DSM-III* criteria. The diagnostic interview was conducted within 2 weeks before lactate infusion. The Hamilton Rating Scale for Anxiety (19) and the Hamilton Rating Scale for Depression (20) were administered to all subjects within 1 week before lactate infusion.

All 22 alcoholic subjects were drawn from an inpatient alcohol treatment program. On admission to the program, patients were asked about symptoms of panic and agoraphobia by a psychiatrist (L.P.) or senior psychiatric resident (D.J.) using the appropriate sections of the Diagnostic Interview Schedule (DIS) (21). Additional questions were added regarding the relationship of these symptoms to intoxication and withdrawal from alcohol and other drugs. Patients with clear-cut spontaneous panic attacks meeting *DSM-III* criteria, at least some of which occurred during prolonged periods of abstinence from alcohol and other drugs, were approached about the lactate infusion study, as were control alcoholic subjects without a history of panic attacks or current axis I psychiatric disorders (except substance use disorders).

Subjects selected for further study had their diagnoses confirmed by using the Anxiety Disorders Interview Schedule (22), were given the Hamilton rating scales for anxiety (19) and depression (20), and underwent lactate infusion at the completion of their 4-week inpatient treatment. The Anxiety Disorders Interview Schedule was administered by a psychiatrist blind to the results of the screening interview (C.F.J.).

Alcoholic subjects undergoing lactate infusion had a mean±SD duration of problem drinking of 17±6 years. All had experienced substantial occupational, marital, or social dysfunction as a result of drinking. Ten of the 12 alcoholics with panic attacks and five of the 10 alcoholics without panic attacks had a history of other substance use disorders, but in all cases alcohol was the drug of choice and use of alcohol far overshadowed use of other drugs.

There were no qualitative differences in alcohol withdrawal history between alcoholics with and without a history of panic attacks. Of the 11 alcoholics with panic attacks for whom alcohol withdrawal history was available, eight had a past history of substantial withdrawal symptoms, none had experienced delirium tremens, and two required benzodiazepines during the first 3 days of the current admission. Of the 10 alcoholics without a history of panic, seven reported past withdrawal symptoms, two had experienced delirium tremens in the past, and three required benzodiazepines during the first 4 days of the current admission.

Of the 12 alcoholics with panic attacks, five had current *DSM-III* panic disorder (three attacks in a 3-week period) at the time of the study, three had a history of panic disorder and current infrequent panic attacks, and four had infrequent panic attacks. All 12 had had at least one spontaneous panic attack in the preceding 3 months. Three had a history of agoraphobia, but none was currently agoraphobic.

Lactate infusions for all subjects were performed in the morning after the subject had fasted overnight and abstained from caffeine and tobacco for at least 3 hours. Subjects undergoing lactate infusion had no history of use of any psychoactive medication in the 2 weeks before the lactate infusion, no serious uncontrolled medical illness, and no psychotic, bipolar, or organic mental disorders. After lying quietly for 30 minutes, the subject had an intravenous line placed in an antecubital vein, a blood lactate level was drawn, baseline heart rate and blood pressure were measured, and baseline rating scales were applied. Normal saline was given as a slow drip for 10 minutes and then at a rate comparable to the subsequent lactate infusion for 5 minutes. Then the infusion was changed to 0.5 M of sodium lactate under single-blind conditions (unknown to the subject but known to the physician in attendance); 10 cc/kg of sodium lactate was infused over 20 minutes. Solutions were warmed to body temperature. The physician performing the infusions (D.S.C.) was blind to the subject's diagnosis during the procedure and until a rating of the subject's lactate response was made. The infusion was stopped immediately in the case of a panic attack if the subject asked to stop.

During the procedure each subject's heart rate was monitored continuously and recorded every 5 minutes. The subjects were asked every 5 minutes to rate their degree of anxiety or fear on a scale from 0 (calm) to 10 ("as frightened as you've ever been") and to rate their panic symptoms using the Acute Panic Inventory (23). The Acute Panic Inventory is a 17-item inventory used to rate symptoms typical of spontaneous panic attacks, such as palpitations, shortness of breath, dizziness, sweating, trembling, confusion, and sense of impending doom, on a severity scale from 0 to 3. In the present study, one item (difficulty doing a job) was omitted, yielding a 16-item instrument with a maximum score of 48.

As in past lactate infusion studies at our center (24), lactate responses were rated as panic, positive, or negative by the physician present during the infusion. A panic response was characterized by sufficient *DSM-III* symptoms beginning or increasing during lactate infusion to meet criteria for a panic attack as well as the abrupt onset of fear that the patients with a history of panic felt to be typical of their spontaneous panic attacks. A positive response was defined as sufficient *DSM-III* symptoms to meet criteria for a panic attack together with an increase in anxiety self-ratings of at least 2 points on the 0–10-point scale to at least moderate levels (4 or higher). A negative response did not meet these criteria.

Blood alcohol levels were obtained for all alcoholic subjects on the day of the lactate infusion and were negative in all cases. Lactate levels were drawn at the time of insertion of the intravenous line (baseline lactate level), at the end of the lactate infusion (peak lactate level), and 30 minutes after termination of the infusion (postinfusion lactate level). L-Lactate was measured enzymatically and electrochemically by using a probe in which hydrogen peroxide produced by oxidation of L-lactate in the presence of L-lactate oxidase and FAD was then converted to oxygen, two hydrogen ions, and two electrons, yielding a current that was linearly proportional to the concentration of L-lactate in the sample.

Chi-square tests were used to perform group comparisons of discontinuous data, and continuous data were compared in the three diagnostic groups by using one-way analysis of variance (ANOVA) with post hoc t tests to determine sources of significant interactions. Comparisons of lactate infusion measures between responders in the group of nonalcoholic patients with panic disorder and the alcoholic patients with panic attacks were performed by using independent group t tests. Lactate levels in the three groups over the three measurement times were compared with repeated measures ANOVA.

RESULTS

The alcoholics without panic attacks in this study were significantly older than the subjects in the two other groups (45.5±6.8 years versus 36.1±10.1 for nonalcoholics with panic disorder and 37.0±3.5 for alcoholics with panic attacks; F=5.0, df=2, 37, p< 0.01). Our past studies have shown no effect of age on lactate response in patients with panic disorder aged 18–65 (24). Among the nonalcoholic patients with panic disorder in the current sample, there was no significant age difference in lactate response, and correlations between age and Acute Panic Inventory scores, anxiety self-ratings, and heart rate showed no significant results or even trends in the data.

TABLE 1. Lactate Levels of Nonalcoholic Patients With Panic Disorder and Alcoholic Patients With or Without Panic Attacks Before and After Sodium Lactate Infusion

	Lactate Level (mmol/liter)					
	Baseline		Peak		Postinfusion	
Diagnosis	Mean	SD	Mean	SD	Mean	SD
Nonalcoholic patients with panic disorder (N=11)	1.1	0.4	4.4	1.0	2.3	0.5
Alcoholic patients with panic attacks (N=6)	1.2	0.5	5.0	1.0	3.0	0.7
Alcoholic patients without panic attacks (N=6)	0.9	0.2	5.5	1.4	2.9	0.6

Alcoholics with panic attacks were more similar to nonalcoholic patients with panic disorder than they were to alcoholics without panic attacks in Hamilton anxiety and depression scale scores. Mean±SD Hamilton anxiety scores were 21.2±6.6 for nonalcoholic patients with panic disorder, 18.3±7.8 for alcoholics with panic attacks, and 8.3±6.5 for alcoholics without panic attacks (F=11.0, df=2, 37, p<0.001). Hamilton depression scores were 13.1±6.1, 15.8±8.2, and 7.2± 5.4 for these three groups, respectively (F=4.6, df= 2, 37, p<0.02).

Alcoholic patients with panic attacks were more likely to have a past history of major depression (10 of 12 subjects) than were nonalcoholic patients with panic disorder (four of 16) or alcoholic patients without panic attacks (five of 10) (χ^2=9.3, df=2, p<0.01), although in many cases the depression had coexisted with heavy alcohol use. No subject currently met criteria for major depression.

Blood lactate levels were drawn for six of 12 alcoholics with panic attacks, six of 10 alcoholics without panic attacks, and 11 of 16 nonalcoholic patients with panic disorder. Mean values for each group at baseline, time of peak symptoms, and 30 minutes after the end of the infusion are shown in table 1. Repeated measures ANOVA revealed significant time effects (F=193, df=2, 40, p<0.0001) but no significant diagnosis or Diagnosis-by-Time effects). The slightly lower mean peak levels in nonalcoholic patients with panic disorder were partially attributable to three patients who terminated the infusion early and thus did not receive the full lactate dose.

Mean baseline, peak, and net peak (peak minus start of lactate) Acute Panic Inventory scores, anxiety self-ratings, and heart rate, as well as mean values for the maximum heart rate change within a 5-minute period, are shown in table 2. At baseline, anxiety self-ratings and heart rate did not differ significantly between groups. Nonalcoholic patients with panic disorder had higher baseline Acute Panic Inventory scores than either of the other two groups (F=3.3, df=2, 37, p<

TABLE 2. Panic Scores, Anxiety Scores, and Heart Rate Before and After Sodium Lactate Infusion of Nonalcoholic Patients With Panic Disorder and Alcoholic Patients With or Without Panic Attacks

	Patients With Panic Disorder (N=16)		Alcoholic Patients					
			With Panic (N=12)		Without Panic (N=10)		F	
Item	Mean	SD	Mean	SD	Mean	SD	(df=2, 37)	Significance
Acute Panic Inventory score[a]								
Baseline	2.2	2.1	0.8	1.4	0.6	1.6	3.3	$p<0.05$
Peak	15.4	9.5	12.9	9.8	4.9	4.7	4.6	—[b]
Net peak[c]	12.4	8.8	10.2	8.1	4.4	3.6	3.5	—[d]
Anxiety self-rating[e]								
Baseline	1.8	1.2	2.1	1.9	1.6	1.6	0.27	n.s.
Peak	5.4	2.8	4.7	3.3	2.0	1.8	4.6	—[f]
Net peak[c]	3.1	2.6	2.5	2.0	0.7	1.0	4.1	—[f]
Heart rate (beats/min)								
Baseline	76.5	13.3	69.0	10.1	70.6	7.2	1.8	n.s.
Peak	95.1	14.3	83.2	12.2	84.6	9.5	2.3	n.s.
Net peak[c]	19.8	9.2	21.7	9.5	17.2	10.7	0.6	n.s.
Maximum increase in 5 minutes	15.9	8.0	13.8	6.5	11.2	6.7	1.3	n.s.

[a] 16 items rated on a scale of 0–3; maximum severity score=48.

[b] Alcoholic patients without panic attacks had significantly lower scores than patients with panic disorder ($p<0.005$) and alcoholic patients with panic attacks ($p<0.05$).

[c] Peak minus start of lactate scores.

[d] Alcoholic patients without panic attacks had significantly lower scores than patients with panic disorder ($p<0.01$) and alcoholic patients with panic attacks ($p<0.08$).

[e] Scale of 0–10: 0=calm; 10="as frightened as you've ever been."

[f] Alcoholic patients without panic attacks had significantly lower scores than patients with panic disorder ($p<0.01$) and alcoholic patients with panic attacks ($p<0.05$).

0.05). Nonalcoholic patients with panic disorder and alcoholics with panic attacks developed significantly higher peak and net peak Acute Panic Inventory and anxiety self-ratings than did alcoholics without panic attacks. There were no significant differences between groups in peak and net peak heart rates or in maximum heart rate changes.

Among the lactate responders, nonalcoholic patients with panic disorder reported peak symptoms 14.2± 5.6 minutes into the lactate infusion and alcoholic patients with panic attacks reported peak symptoms 17.6±3.1 minutes into the lactate infusion. These values were not significantly different according to t test. Six of the 16 nonalcoholic patients with panic disorder and one of the 12 alcoholics with panic attacks asked to stop the infusion early because of panic symptoms.

Of the 16 nonalcoholic patients with panic disorder, eight had a panic response, four had a positive response, and four had a negative response. Five of the 12 alcoholics with panic attacks had a panic response, two had a positive response, and five had a negative response. Of the 10 alcoholics without panic attacks, none had a panic response, one had a positive response, and nine had a negative response. Overall lactate response rates were significantly higher in the two groups with panic attacks than in the group without panic attacks ($\chi^2=11.2$, df=4, $p<0.02$). Nonalcoholic patients with panic disorder and alcoholics with panic attacks did not differ significantly in their lactate response rates.

DISCUSSION

In this study, alcoholics with panic attacks differed significantly from alcoholics without panic attacks and more closely resembled nonalcoholic patients with panic disorder in their response to sodium lactate infusion. This supports past findings of specificity of lactate vulnerability for panic attacks and suggests that panic attacks in alcoholics are similar to those in nonalcoholic patients with panic disorder, at least in their reproduction by a lactate challenge test.

In our sample, only one of the 10 alcoholics without panic attacks responded to lactate infusion. This response rate is similar to that of nonpsychiatric control subjects and that of psychiatric patients without a history of panic attacks (17). In contrast, alcoholics with panic attacks were more similar to nonalcoholic patients with panic disorder in baseline anxiety and depression rating scale scores, overall lactate response rate, and Acute Panic Inventory scores and self-rated anxiety with lactate. Alcoholics with panic attacks tended to report a later onset of peak lactate-induced symptoms and to be less likely to ask to stop the infusion early than patients with panic disorder, but these differences did not reach statistical significance. There were no major differences in lactate metabolism between groups, at least as reflected by blood L-lactate levels. The lack of significant differences in heart rate reactivity between groups is consistent with past studies of patients with panic disorder and control subjects at our center (24).

Our results differ from those of George et al. (unpublished 1987 data), who found a higher rate of lactate-induced panic in female patients with panic disorder who were also adult children of alcoholics than in male alcoholics with panic attacks. Their panic rate in female patients with panic disorder who were also adult children of alcoholics was very much higher than that in any of our subject groups. The discrepancy between our results and theirs may be due to differences in the patients studied, to the fact that in their study a request to stop the infusion was used as the criterion for lactate-induced panic (George, personal communication), or to higher lactate vulnerability in patients with panic disorder who are also adult children of alcoholics. Only four of our 16 nonalcoholic patients with panic disorder had an alcoholic first-degree relative; three of these four patients panicked with lactate infusion.

Our results support the general observation that lactate vulnerability is specific for the phenomenon of panic attacks regardless of a coexisting diagnosis (16, 17). Furthermore, it appears that carefully diagnosed panic attacks in alcoholics resemble those of nonalcoholic patients with panic disorder in their reproducibility with sodium lactate infusion. This, in addition to the lack of lactate responsivity in alcoholic subjects without panic attacks, supports the view that panic attacks in alcoholics, whatever their etiology, represent an important coexisting condition rather than merely confusion with acute withdrawal symptoms or manifestations of prolonged or subacute withdrawal.

Despite the similarity in lactate responsivity in alcoholics with panic attacks and nonalcoholic patients with panic disorder in this study, only 58% of the alcoholics with panic attacks responded to lactate, compared with 10% of alcoholics without panic attacks. Thus, the sensitivity of this test in alcoholic subjects is low. Nevertheless, a positive or panic response to lactate may add helpful information in some cases in which the alcoholic patient's history is unclear or the diagnosis of panic attacks is uncertain. Follow-up and treatment studies of lactate-vulnerable alcoholics with panic attacks may clarify the clinical significance of this test in identifying alcoholics with persistent panic attacks who are responsive to antipanic medication.

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Exploring the Multidimensional Aspects of Grief Reactions

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The authors explored the multidimensional aspects of early grief reactions in 201 relatives and close friends of victims of accidental deaths, suicides, homicides, and sudden natural deaths. A principal components analysis of a grief reaction measure revealed four factors: depressive symptoms, preservation of the lost object, suicidal ideation, and decedent-directed anger. The authors suggest that certain features which have been associated mostly with pathological grief (e.g., difficulty relinquishing the lost object) may be present in many, if not most, of the general population during bereavement and that pathology may best be determined by measuring the frequency and intensity of these features.

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While the study of grief continues to generate considerable interest in the literature, investigators still struggle in operationalizing and validating the construct of grief (1). Clinically, the signs and symptoms of grief first described by Lindemann (2) (somatic distress, preoccupation with the image of the deceased, guilt, hostile reactions, and loss of conduct patterns previously influenced by the deceased) have proven robust when subsequently subjected to theoretical and empirical scrutiny. In fact, Lindemann offered a better representation of the possible multidimensionality of grief reactions than many more recent, empirically oriented investigators.

Various efforts have been made to develop better measures to assess grief reactions (1, 3–7). Although the developers of these measures more broadly operationalized grief by including items pertaining to depression, anger, guilt, pining, fear of dying similarly, and difficulty in accepting the loss, only Sanders et al. (3) developed empirically derived subscales that reflect the multidimensionality of grief reactions. Unfortunately, the inventory is long and some of the subscales have poor interitem consistency. Krupnick and Horowitz (5) developed a content analysis rating manual that established themes on an a priori basis (i.e., without empirically determining if the themes actually represent discrete variables) with which to rate clinical material. However, since this technique is time-consuming, it cannot be easily employed in large-scale studies of subjects not receiving extensive evaluation or therapy. Others (1, 4, 6) have compiled diverse items into unidimensional measures of grief.

In this article we describe the analysis of a grief reaction measure that expands on a list of positive symptoms of bereaved subjects reported by Clayton and Darvish (4) and discuss its implications for a multidimensional understanding of grief reactions. This research was part of a more comprehensive study of early grief reactions according to the four modes of death (natural, accidental, suicidal, and homicidal) in non-Hispanic white, black, and Hispanic Americans. The purpose of this analysis was to derive a brief multidimensional grief reaction measure with which to later make comparisons on the basis of mode of death and race ethnicity.

METHOD

The respondents were 201 close relatives or intimate friends of victims of violent or sudden natural death who agreed to be interviewed about their bereavement; there were 175 women and 26 men. A random sample of accidental death, suicide, and homicide victims 14 years old or older was drawn weekly from the city of Los Angeles and the unincorporated area of East Los Angeles by a project staff member. Potential respondents were identified through the Los Angeles County Medical Examiner/Coroner's Office. Victims of natural deaths were selected in the same manner, except samples were drawn at approximately 3-week intervals from the medical examiner/coroner's office. Several criteria were imposed on the decedents who had died natural deaths. First, each decedent must have died in the course of daily routine, must not have been under the immediate care of a physician, and must not have had any contact with a health facility related to the cause of death in the recent past before the death. This constraint was imposed to rule out

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prolonged terminal illnesses and severe disabling disorders. Secondly, the decedent could not be older than 70 years of age. This constraint was imposed to reduce the likelihood that those who had died natural deaths had been very elderly or had had numerous age-related health impairments. Finally, the cause of death could not be related to alcohol. This third constraint was imposed to avoid an atypical relationship between decedent and respondent and to eliminate alcohol as an agent of suicide. For all modes of death, the race ethnicity of the respondents was established by self-identification.

Among all those initially contacted, the rejection rate was approximately 55% for cases involving natural death and 44% for cases of violent death. An additional limiting factor in the sampling process was the cases in which there were no potential respondents. They constituted approximately 19% of the population pool.

The overall mean age of the respondents was 42.6 years (range=16–79). The mean ages of the groups associated with accidental death, suicide, homicide, and natural death were comparable; the suicide group had the highest mean age (44.4 years), and the homicide group had the lowest (41.2 years).

The overall mean age of the decedents was 39.7 years (range=14–92). The mean age of the decedents who had died natural deaths was considerably higher (53.4 years) than the mean ages of those who had died violent deaths (accident victims, 39.9 years; suicide victims, 42.8 years; homicide victims, 31.9). However, the victims of natural death were relatively young, suggesting that the natural deaths were most likely untimely.

The mean number of days from the death to the time of the interview was 49.4 (range=19–107). With regard to mode of death, the largest difference (9 days) occurred between the means for the accident group (44.7 days) and the homicide group (53.6 days).

In the cases of both violent and natural deaths, letters were sent to the potential respondents informing them of the study, asking their cooperation, and telling them that someone would soon be calling them to request their participation. The letter was mailed about 2 weeks after the death in the case of accidental death, suicide, or natural death and about 4 weeks after a homicide (the latter at the request of the Los Angeles sheriff's office and police department). A telephone call was made by a project interviewer after delivery of the letter to request voluntary participation and to arrange an appointment for an interview.

After we obtained written consent, an interview was conducted at the respondent's home unless the person preferred to be interviewed in the project office or at another location. Each interviewer had a master's degree in psychology or a related field and had received training in interviewing and counseling the bereaved before becoming involved in the bereavement project. Two of the interviewers were fluent in Spanish.

A grief reaction measure and background information questions were administered to the respondents. The grief reaction measure was largely adapted from a list of positive symptoms recorded by Clayton and Darvish (4). Various modifications were made to the list. Additional items were incorporated to reflect 1) Stone's grief questionnaire items (8) that differentiated subjects grieving for suicide victims from subjects grieving for decedents who had died from other causes, 2) the findings of Bowlby (9–11), Parkes (12, 13), and Volkan (14, 15) about attempts by bereaved subjects not to relinquish emotionally the lost objects, and 3) expansion of the Clayton and Darvish items dealing with blame, fear, and anger so as to apply them to the different modes of violent death. The list was also converted from a "present/not present" endorsement format to a 4-point Likert scale, ranging from 0 ("not at all") to 3 ("all of the time"), to increase the sensitivity of the measure. Finally, the questionnaire instructed the respondent to report how he or she felt during the month before the death and in the period since the death. Items specifically concerning the death were excluded from the section of the questionnaire covering the time before the death.

The background information questions and the grief measure were translated into Spanish by initially pooling translations by several fluent Spanish speakers of different Hispanic heritage and then using a consensual method to determine the final set of translated items.

RESULTS

A principal components analysis with a varimax rotation was employed to examine the underlying structure of the different dimensions of the grief reactions and to develop factor-derived subscales from the post-death measure. Only factors with eigenvalues of 1 or above (an estimate of the importance of individual factors) and item loadings of 0.40 or higher (i.e., 16% of the variance for a factor) were used to derive the final factor solution, which consisted of 20 items and four factors. The original list comprised 37 items. In the final 20-item solution, factor 1, labeled "depressive symptoms" because the symptoms represent the neurovegetative signs and symptoms of a clinical depression, accounted for 58% of the variance. As a factor-derived subscale, it clearly reflects the heavily depression-oriented content of the Clayton and Darvish list (4). Factor 2, labeled "preservation of the lost object" because it describes an apparent reluctance to relinquish the lost object (i.e., the decedent), accounted for 16% of the variance. Factor 3, labeled "suicidal ideation" for obvious reasons, accounted for 15% of the variance. Factor 4, labeled "decedent-directed anger," accounted for 11% of the variance.

Table 1 shows these factor-derived subscales along with their corresponding Cronbach alpha coefficients, the percentages of the variance for which the factors accounted, the loading for each item in the factors (i.e., the correlation of each item with the factor), and the mean±SD ratings. Although factor 4 consisted of only

TABLE 1. Factor-Derived Subscales of a Grief Reaction Measure Based on Responses of 201 Relatives and Close Friends of Victims of Sudden or Unnatural Deaths

		Rating[b]	
Subscale Item[a]	Loading	Mean	SD
Factor 1: depressive symptoms (alpha=0.87, 58% of variance)		1.6	0.8
Loss of appetite	0.55	1.5	1.2
Fatigue or being tired	0.44	1.8	1.2
Poor memory, forgetting things	0.53	1.3	1.2
Loss of interest in normal work and recreational activities	0.63	1.5	1.3
Difficulty concentrating	0.78	1.5	1.2
Feeling restless	0.63	1.7	1.2
Trouble falling asleep at night	0.72	1.7	1.2
Waking up too early in the morning	0.56	1.5	1.3
Other problems with sleep (e.g., restless sleep, nightmares)	0.61	1.2	1.2
Feeling low, depressed, sad, despondent, discouraged, or blue	0.57	2.2	1.0
Factor 2: preservation of lost object (alpha=0.72, 16% of variance)		0.5	0.6
Having visions of the decedent	0.46	0.6	1.0
Hearing the voice of the decedent	0.54	0.4	0.8
Having felt the decedent touch you	0.51	0.2	0.6
Hearing the decedent's footsteps, movements, etc. (as distinguished from hearing his/her voice)	0.67	0.3	0.8
Feeling the decedent's "presence" or "spirit" around you or in the house	0.69	1.0	1.2
Factor 3: suicidal ideation (alpha=0.69, 15% of variance)		0.6	0.7
Wishing you were dead	0.70	0.6	1.0
Feeling hopeless	0.57	0.9	1.1
Thinking about killing or harming yourself	0.55	0.2	0.6
Factor 4: decedent-directed anger (alpha=0.76, 11% of variance)		0.6	0.9
Blaming the decedent (for any reason)	0.77	0.7	1.0
Feeling angry at the decedent (for any reason)	0.77	0.5	0.9

[a] Alpha for 20 total items=0.86.
[b] 0=not at all, 3=all of the time.

two items, it was retained as a subscale because it emerged from other items that included blame and anger directed at targets other than the decedent (e.g., other people, self, or situation) and had potential theoretical significance. Cronbach alphas were included because the principal components analysis was used to develop a preliminary factor-derived grief reaction scale. The Cronbach alpha coefficients are measures of reliability (i.e., the consistency of responses to all items in each of the factor-derived subscales), and as can be clearly seen, they were within the acceptable range. It should be noted that the two items that loaded on factor 4, decedent-directed anger, had very high loadings. Thus, it appears that this factor may be quite viable and was limited only by the lack of inclusion of items covering decedent-directed anger.

To arrive at a clearer understanding of how prominent the aspects of grief represented by the subscales were in our sample, the percentages of respondents who gave a Likert rating of 1 ("a little of the time") or higher to at least one item in each subscale were computed. These percentages were as follows: depressive symptoms, 99%; preservation of the lost object, 64%; suicidal ideation, 56%; and decedent-directed anger, 43%.

To determine if there were sex differences on the factor-derived grief reaction subscales, a nonparametric statistic, the Brown-Forsythe F^* (16), was used because of the large difference in the numbers of male and female respondents. Comparisons were made for both the pre- and postdeath time periods, but a predeath measure for preservation of the lost object was not possible since there were no analogous items for this time period. For the time before the death, significant differences in the mean ratings of the men and women were obtained for depressive symptoms (men=0.35, women=0.57; $F^*=6.19$, df=1, 46, $p<0.05$) and decedent-directed anger (men=0.25, women=0.52; $F^*=10.00$, df=1, 60, $p<0.01$). Significant differences after the death were found for depressive symptoms (men=1.24, women=1.63; $F^*=5.48$, df=1, 60, $p<0.05$) and preservation of the lost object (men=0.24, women=0.55; $F^*=8.58$, df=1, 63, $p<0.01$). The means for decedent-directed anger were similar (men=0.60; women=0.61).

DISCUSSION

The results from this study clearly illustrate the prominence of depression in grief, as indicated by the emergence of the strong depressive symptoms factor (endorsed by 99% of the sample) and the suicidal ideation factor (endorsed by 56% of the sample). Both of these factors are consistent with the depression characteristic of the second phase of the grief process (yearning and searching for the lost object) as conceptualized by Bowlby (11) and Parkes (12). Given the mean number of days from the date of death to the date of interview, it would be anticipated that the respondents in this study were most likely going through the second phase of the grief process. The emergence of factor 2 (preservation of the lost object), which was endorsed by 64% of the sample, confirms the hypothesis of Bowlby and Parkes that attempts by the bereaved, whether conscious or not, to regain or preserve the lost object play a crucial role during the second phase of the grief process.

The respondents provided numerous anecdotal examples of their attempts to either preserve or relinquish the lost objects. These ranged from what may be considered pathological attempts to what might be considered adaptive ways of getting through the painful loss. One example of the struggle to relinquish the lost object came from a Hispanic woman whose husband had died a natural death; she reported to the interviewer (L.A.V.) that she still continued to cook as if her husband were present, laying two dishes out for him and herself and paying particular attention to serving food she knew he preferred. She was still doing so even approximately a month and a half after his death, when the interview took place. Outside of the house, where he had been gardening at the time of his fatal heart attack, she had erected a small altar, which she tended daily. In a sense, most of her daily routine centered on her attempts to keep from having to relinquish her dead husband. Another Hispanic woman had known her live-in boyfriend less than 6 weeks when he unexpectedly shot himself in the head in the presence of her and her young daughters. She was still devastated at the time of the interview. Upon termination of the interview, she asked the interviewer (L.A.V.) to view a small altar she had erected for her boyfriend atop a dresser. The altar was decorated with various pictures, personal objects and mementos of the decedent, and a folded handkerchief lying at the foot of a cross surrounded by lighted candles. She mentioned to the interviewer that this handkerchief was her most esteemed possession. With a certain religious deference, she opened up the handkerchief to reveal dried parts of her boyfriend's cranium, which she had collected from the room where he had committed suicide.

An example of an adaptive effort to relinquish the lost object was given by a middle-aged black woman whose husband had died unexpectedly of a heart attack while cleaning out their recreational vehicle. She reported to the interviewer (L.A.V.) that she had had much difficulty going to sleep at night shortly after the death because of the immense loss she felt. She described a series of measures she had taken to help her get over these difficult moments. She mentioned that at first she weighed down the other side of the bed with stuffed clothing belonging to her husband. She noted that the sense of weight along with her feeling that her husband was still present gave her the necessary peace of mind to be able to sleep in the early weeks after the death. She noted that eventually she was able to remove the stuffed clothing and use only a pillow, which she would hug during the night when the pangs of loss were most severe. At the time of the interview, which was approximately a month and a half after the death, she reported that she no longer required the pillow and that momentary recollections of her husband being with her sufficed to provide her the necessary emotional tranquility to sleep. When she thought back on what she had told the interviewer, she became embarrassed and commented that he must think that she was crazy to have taken such measures to help her sleep at night. From the qualitative data available, it appears that what is normal and what is pathological is determined by the extent to which the griever attempts to preserve or regain the decedent. It is clear that this aspect of grief is likely to play an important role in a person's ability to accept the loss of a loved one. Intervention in both normal and severe grief reactions should focus more specifically on how this aspect of grief is being resolved.

Emergence of a factor involving decedent-directed anger is also consistent with Bowlby's (11) and Parkes' (12) contention that anger is not uncommon in the normal grief experience. However, anger as a factor did not surface as general and nonspecific but, rather, as specifically directed at the decedent, which may also account for the endorsement of the factor by only 43% of the sample. The emergence of this factor suggests that a specific feature of the grief process in its second phase is decedent-directed anger and that such anger exists in a form distinguishable from other nonspecific manifestations. This factor appears to buttress the clinical impression of many grief counselors that anger at the decedent is an important, if not necessary, aspect of the grief process regardless of the mode of death. However, an argument could be made that since all the deaths in this study were sudden and untimely, emergence of such a factor is a result of the unexpected nature of these deaths, which makes it more likely that the bereaved will attribute some causality to the decedent. Such an alternative hypothesis cannot be ruled out in the present study.

From a theoretical standpoint, it is likely that decedent-directed anger may be an essential development that helps the griever finally relinquish the lost object. Being able to express anger at the decedent in a fully conscious manner may represent important progress in the acceptance of the death and the realization, if also painful, that attempts to retain the lost object are futile and unnecessary. It is possible that the nonspecific or generalized manifestations of anger noted by Bowlby and Parkes represent early precursors of the development of decedent-directed anger. As long as the anger remains generalized, the griever may continue to struggle to resolve the second phase of grief. Failure to develop decedent-directed anger may represent the griever's unreadiness or unwillingness to accept the fact that the decedent has been lost and must be emotionally relinquished. From this standpoint, it could be hypothesized that preservation of the lost object and decedent-directed anger operate inversely of each other. A longitudinal study would be necessary to test this hypothesis. The relatively early stage in the grief experience of our sample may explain why only 43% of the sample endorsed items involving decedent-directed anger.

The study offers certain refinements not present in many grief studies. First, the sample was not drawn from the population of psychiatric patients. Second, all four modes of death were represented. Third, the sample consisted of three distinct racial ethnic groups. Fourth, the mean times between date of death and date of interview were equivalent for the groups defined by either mode of death or racial ethnic group. Fifth, the mean ages of the four mode of death groups were similar. Sixth, all respondents were allowed to respond in a manner that allowed them to indicate the frequency and intensity with which they experienced each sign or symptom.

Because the sample was derived from a general, nonpsychiatric population, the study has certain limitations. First, the high rejection rates limit the generalizability of the results. Second, the high number of cases in which there were no potential respondents (19%) further limits the generalizability of the results. However, since inability to locate a respondent was more often the case in homicides and sudden natural deaths of the homeless, data on these subpopulations may be characteristic of atypical groups (i.e., those in fear of retaliation from aggressors if identified and/or those estranged from their families). Third, the underrepresentation of men in the sample makes it difficult to study grief reactions in men. In part, the low rate of participation by men was due to their lower likelihood to volunteer for the study and to the greater likelihood that the next of kin listed in the records of the Los Angeles County Medical Examiner/Coroner's Office was female (especially mothers and wives in the case of homicides, most victims of which were male). Fourth, the respondents were not homogeneous, largely because accidental deaths and homicides tend to occur in younger populations than do sudden natural deaths and suicides. Thus, the respondents in the accident and homicide groups were more likely to be parents. Fifth, since this study did not include natural deaths that were prolonged or expected, it is not possible to suggest that those grieving for friends or relatives who had prolonged or expected natural deaths experience grief in the same manner.

The sex differences in depressive symptoms and in preservation of the lost object after the death indicate the need for caution in applying these results to men. On the average, the men in this sample reported less depression and preservation of the loss object than the women. It is noteworthy that while the sex difference in depressive symptoms for the predeath time period carried through the postdeath period, the sex difference in decedent-directed anger did not. After the death, the men and women were equally angry. Although sex comparisons generally have suggested that sex is not as significant a variable as might be expected (7, 17–20), certain investigators (21–24) have pointed to some significant sex differences. In particular, Glick et al. (23) and Sanders (21) have suggested that widowers display fewer outward signs of grief.

The present study illustrates that grief reactions are multidimensional. It also suggests that certain features which have been associated mostly with pathological grief may well be present in many, if not most, of the general population during bereavement and that pathology may be best determined by measuring the frequency or intensity of these features (e.g., either absent or too frequent and intense).

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Family Planning Needs of Female Chronic Psychiatric Outpatients

John H. Coverdale, M.B., Ch.B., and John A. Aruffo, M.D.

The authors investigated the pregnancy outcomes, contraceptive behavior, and contraceptive needs of 80 female chronic psychiatric outpatients. Thirty-one percent of the patients reported they had had induced abortions. Of 75 children born, 60% were being reared by people other than the mothers. Thirty-three percent of the patients who had had intercourse during the preceding year and had not wanted to become pregnant reported not having used contraception at the time of last intercourse. The authors discuss the special contraceptive needs of chronic psychiatric patients and encourage psychiatrists to inquire about patients' family planning practices.

(Am J Psychiatry 1989; 146:1489–1491)

Studies on the family planning needs of chronic psychiatric patients have been infrequent and have been carried out only with psychiatric inpatients (1–3). The family planning needs of chronic mentally ill women who are either fully or intermittently resident in the community are considered to be even more acute (4). The costs of unwanted pregnancies in this population may be considerable. Chronic psychiatric patients are also often characterized by poor judgment. In addition, emotional or cognitive deficits or thought disorders may detract from their ability to obtain and use relevant family planning information.

The present study set out 1) to determine the contraceptive needs of a sample of chronically ill female psychiatric outpatients in relation to their sexual and contraceptive behavior and in relation to their attitudes toward becoming pregnant and 2) to determine their history of pregnancy outcomes.

METHOD

Eighty female patients, aged 18 to 40 years, were interviewed at a publicly funded county mental health clinic. All patients admitted to the clinic satisfied criteria for priority service that were mandated by the state and applied by qualified mental health professionals. These included 1) the presence of a chronic mental disorder of at least 2 years' duration and present or potential dangerousness and/or present or potential dependence on external community resources because of mental disorder or 2) the presence of a mental disorder of less than 2 years' duration and present dangerousness and/or dependence and at least one previous psychiatric hospitalization. All patients who were present at the clinic during various time periods (which were determined weekly by the interviewers' availability) were asked for their cooperation and informed consent. The interviews took place over 9 months and were conducted privately by us in an interviewing room. Twelve patients who were asked to participate either refused or were deemed too psychotic.

We administered the Mini-Mental State examination (5), which is a widely used and validated questionnaire that screens for cognitive function. The patients then provided demographic, obstetrical, and gynecological information in the 30-minute interview. (We also collected information on the patients' knowledge of AIDS, but this is not reported here.) The psychiatric diagnoses that had been made by the psychiatric staff of the clinic were confirmed by the investigators through retrospective chart review. The interview schedule was structured, and the questions were designed to not be leading and to use language appropriate to about the lowest of the educational levels of the patients. When the patients were asked about whether they wanted to become pregnant, the answers were categorized as "yes," "no," or "maybe" (unsure). Patients who responded "yes" or "maybe" were asked how soon they might like to become pregnant, and the answers were coded "less than 1 year," "more than 1 year," or "after marriage." Answers that showed looseness of associations or were obviously delusional were categorized as "bizarre."

The mean age of the 80 patients was 31 years (range=18–40), and the mean level of education com-

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TABLE 1. Psychiatric and Medical Information on 80 Female Chronic Psychiatric Outpatients

Characteristic	N	%
Diagnosis		
Schizophrenia	40	50
Schizoaffective disorder	9	11
Major affective disorder		
Bipolar disorder	12	15
Major depression	10	13
Other	9	11
Mini-Mental State score≥24	75	94
History of psychiatric hospitalization	76	95
Hospitalization within the past year	37	46
Two or more hospitalizations	65	81
Pelvic examination		
Within the past 3 years	62	78
Over 3 years ago	13	16
Never	5	6
Sexual orientation		
Heterosexual	70	88
Bisexual	6	8
Did not specify	4	5
Number of "bizarre" responses		
0	56	70
1	13	16
2–4	8	10
5 or more	3	4

pleted was 12th grade (range=3rd grade to college). Forty-seven subjects (59%) were white, and 33 (41%) were nonwhite, predominantly black. The most common religious affiliations were Baptist (N=27) and Catholic (N=14). Fifty-five (69%) of the patients were receiving financial assistance, while 14 (18%) were currently employed. Thirteen (16%) were currently married, and 41 (51%) had been married at least once.

The psychiatric information obtained is provided in table 1. The most common axis I *DSM-III* diagnoses were chronic schizophrenia, schizoaffective disorder, and affective disorders. Other diagnoses included substance abuse and anxiety disorders. Scores on the Mini-Mental State examination ranged from 19 to 30, and 94% of the patients scored 24 or higher, indicating normal cognitive function. Ninety-five percent of the patients had been hospitalized in the past, and 46% had been hospitalized within the past year. Eighty-one percent had had two or more psychiatric hospitalizations. Sixteen percent reported that their last pelvic examination was more than 3 years ago, while 6% denied ever having had a pelvic examination. No patients reported exclusive homosexuality. Finally, most patients made no "bizarre" comments.

RESULTS

Of the 80 patients, 58 (73%) reported having been pregnant at least one time; 18 (23%) had had one or more miscarriages, 25 (31%) had had one or more induced abortions, and 36 (45%) had had live births. Of the 75 children who had been born to the chronic psychiatric patients, 1% (N=1) had died, 5% (N=4) had grown up and were living independently, 33% (N=25) were being reared by their biological mothers, and 60% (N=45) were being reared by others, most commonly the child's father or an adoptive family. For the 58 patients who had been pregnant, no relationship was found between diagnosis (schizophrenia or schizoaffective disorder versus other) and history of an abortion ($\chi^2=0.79$, df=1, $p>0.05$). Nor was there a relationship for those who had had live births between diagnosis and surrendering a child to be reared by others ($\chi^2=2.86$, df=1, $p>0.05$).

The patients were asked when they last had had sexual intercourse. Fifty-eight (73%) indicated that they had had sexual intercourse within the last year. One patient said she had been raped within this time but otherwise had not had sexual intercourse, and she is not included in this group. Of the 58 who had had intercourse within the last year, 42 (72%) reported that this had occurred within the last 3 months. Forty-three (74%) of the 58 indicated that they would not like to become pregnant within the next year (even though some of them indicated that they might like to become pregnant later or after marriage). Excluded from this group were two patients who indicated they were unsure about wanting to become pregnant within the next year and one patient who said she was currently pregnant.

The contraceptive methods used at last heterosexual intercourse were determined for the 43 patients who reported intercourse within the preceding year and did not want to become pregnant. Tubal ligation (N=9), intrauterine device (IUD) (N=5), and condom (N=5) were the most frequently used methods. The other methods used included the oral contraceptive pill (N=3), cream, jelly, or foam (N=2), the diaphragm (N=2), the rhythm method (N=1), and hysterectomy (N=1). Also, while one patient did not herself use contraception, she reported that her sexual partner had had a vasectomy. Of the 43 patients in this group, 14 (33%) stated they had not used birth control at time of last intercourse. Furthermore, five of the patients who said they were protected at the time of last intercourse indicated that there had been times within the preceding year when a contraceptive method had not been used. For the patients who did not want to become pregnant and who had had intercourse within the last year, no relationship was found between diagnosis (schizophrenia or schizoaffective disorder versus other) and the use of birth control at time of last intercourse ($\chi^2=0.28$, df=1, $p>0.05$).

DISCUSSION

The family planning needs of chronic female psychiatric patients should be understood in relation to their pregnancy outcomes. Thirty-one percent of the patients in this study reported at least one induced abortion in the past. In addition, of the 75 live babies born, 60% (N=45) were being reared by people other than the mothers. These figures may reflect the difficulty some chronic psychiatric patients have in coping with the stress of parenthood.

A significant number of patients were found to be at special risk of unwanted pregnancies. Thirty-three percent of the patients who were sexually active and who said they did not want to become pregnant reported that they had not used birth control at the time of last intercourse. These are patients clearly in need of family planning, counseling, and contraception. Abernethy (3) found that 30 of 60 female inpatients had not used contraception at the time of last intercourse. However, she did not differentiate patients who wanted to become pregnant from those who did not or from those who were unsure. It should also be noted that since 22% of the patients in our study reported that they had not had a pelvic examination within the last 3 years, psychiatrists have an opportunity to intervene in improving patients' routine gynecological care as well as in family planning.

In choosing contraceptives, one must consider the high degree of compliance needed for the oral contraceptive pill to be effective, which may contraindicate its use for some patients. Cream, jelly, foam, and condoms may be effective when used consistently. However, several of the chronic psychiatric patients indicated that they did not use these methods consistently. Condoms serve a double function in that they also reduce the chance of sexual transmission of the acquired immune deficiency syndrome (AIDS) and other sexually transmitted diseases. With regard to the IUD, it is worth considering that some schizophrenic women may have unusually high pain thresholds and therefore may not respond as anticipated to early symptoms of pelvic inflammatory disease. Tubal ligation, while most effective, should be considered irreversible. What is not known is how the patients with tubal ligations in our study were selected for this procedure and whether they made the decision or whether it was made for them. Further research could explore the role of the psychiatrist in this process. Although it was found that medroxyprogesterone had not been prescribed for any of these patients, the new injectable contraceptive norethindrone may provide protection for up to 3 months, and investigation of its usefulness for chronic psychiatric patients, should it become available, may be warranted.

This is the first study of which we are aware that explores chronic psychiatric outpatients' family planning needs. Many of the patients had had abortions or had given up children for others to raise. A significant number engaged in unprotected sexual intercourse despite indicating they did not want to become pregnant. Psychiatrists are often these patients' only contact with the health care system. These findings indicate that there is a need for psychiatrists and other mental health professionals to routinely inquire about the family planning practices and needs of chronic psychiatric patients.

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The Challenge of Relational Diagnoses: Applying the Biopsychosocial Model in *DSM-IV*

Group for the Advancement of Psychiatry Committee on the Family

The meaningful application of the biopsychosocial model in psychiatry requires explicit attention to the relational or interpersonal level of functioning. Family-oriented researchers and clinicians recommend that, despite pressures for early publication of DSM-IV, *the time has come to give a definitive place to relational syndromes in psychiatric nosology.*

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In Paul Fink's address as incoming President of APA (1), he sounded a challenge to "integrate the many factions of contemporary psychiatry" through "revitalizing" the application of the biopsychosocial model. As a correction for the tendency to take one of three constricted, unidimensional paths (biological, psychological, or social), Fink argued that the more comprehensive biopsychosocial model urgently needs to be firmly incorporated into our clinical practice, education, and research and not be used merely as a password or slogan.

As psychiatrists interested in families and larger systems, we believe that the construction of *DSM-IV* provides a major test case of U.S. psychiatry's ability and willingness to work toward a genuine multidimensional view of human problems. In order for *DSM-IV* to be a distinctive advance over *DSM-III-R,* these additional perspectives should be elicited, discussed, and evaluated, preferably with less "rushing" than the present 1992 publication schedule requires (2). As members of the Group for the Advancement of Psychiatry (GAP) Committee on the Family, we are concerned that what once held promise as an "open process" has become prematurely narrowed.

In our view, a defect of the current diagnostic manual is the explicit restriction to syndromes that occur "in a person." We recommend recognition of syndromes that are best defined and identified as occurring between persons, as relational or interpersonal syndromes. These relational syndromes often entail serious personal dysfunction and warrant inclusion as mental disorders (3, 4).

At present, the difficulty of trying to maintain a strictly individual-based nomenclature is recognized only within the inadequate miscellany called the V code supplement to axis I: conditions not attributable to a mental disorder that are a focus of attention or treatment. The V code relational disorders lack diagnostic criteria and are vaguely labeled, for example, as marital problem and parent-child problem. The V codes are not accepted by the profession (or by third-party payers) and have no legitimacy as psychiatric disorders. Incest, domestic conflict and violence, and the family burden caused by the illness of a family member are striking, common, diverse examples of serious relational problems that clearly need to be major concerns of psychiatric attention, treatment, and prevention (5–7). Compared with the distress and disability they incur, these syndromes remain neglected—a situation reinforced by the lack of a place where such problems are meaningfully identified in our official diagnostic and statistical manual (4).

The *DSM-III* approach requires individual-based diagnoses for relational disorders and thereby misdirects assessment and focused treatment away from the cou-

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ple, family, or other relational systems in which dysfunction is most pivotally present. Critics have argued that an individual dysfunction can usually be diagnosed as a component or as an aftermath of relational problems. Even when this is so, the relational context for prevention and crisis intervention is overlooked or underemphasized if such disorders are diagnosed only within individual persons (8–10). Just as personality (axis II) and physical (axis III) diagnoses may be given in addition to axis I diagnoses, so should relational disorders be recognized and given comparable status, perhaps as a distinctive section of axis I, not with the present, indiscriminate V codes.

Furthermore, we believe that *DSM-IV* should include an upgraded axis IV in which a more adequate description of the supports and stressors of families and social networks can be dimensionally assessed in relation to the syndromes of axes I, II, and III (11–13). Additionally, textual changes specifically noting frequent relational and family issues and describing the research-based and clinically known family factors influencing prognosis and treatment decisions for each of the traditional axis I and II diagnoses can and should be introduced into *DSM-IV* (14–21).

For a number of reasons it was impossible to incorporate the information derived from family and "systemic" perspectives into *DSM-III* and *DSM-III-R*. We are deeply concerned that the pressure of a 1992 deadline for the writing and publication of *DSM-IV* may similarly preclude a full consideration and inclusion of these perspectives. They cannot and must not be allowed to wait for the far distant appearance of *DSM-V*. To build a broad base of consensus that will permit adequate attention to them now, the GAP Committee on the Family has met with representatives from the American Family Therapy Association, the American Association for Marriage and Family Therapy, and the American Psychological Association. We are pleased to inform readers of the *American Journal of Psychiatry* that clinicians and researchers working in this field have moved beyond sectarian and parochial concerns; areas of broad agreement have evolved about family typology and about dimensional attributes of interpersonal relationships that merit incorporation into the next *DSM* (22–27). Collaboratively, a coalition of major researchers and experienced clinicians in the family research and therapy field are now reviewing drafts of proposals such as those briefly mentioned here and are planning to conduct field trials to document their usefulness (28).

We believe that explicit attention to relational dysfunctions and disorders will help *DSM-IV* to reflect current, multilevel system concepts that are embodied in the biopsychosocial medical model and that will enable us to carry out teaching, research, and clinical practice appropriately and comprehensively. The question remains: Can U.S. psychiatry respond adequately to the challenge of fulfilling the potential implied by the biopsychosocial model?

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Adjunctive Imipramine Maintenance Treatment in Schizophrenic Patients With Remitted Postpsychotic Depression

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Ten patients with histories of postpsychotic depression responsive to adjunctive imipramine added to fluphenazine decanoate and benztropine underwent a double-blind trial of imipramine discontinuation 6 months after responding to the adjunctive imipramine. Discontinuation of imipramine was associated with depressive relapse.

(Am J Psychiatry 1989; 146:1495–1497)

Recently it has been demonstrated that certain patients with schizophrenia or schizoaffective disorder whose flagrant psychotic episodes have resolved but who subsequently suffer from postpsychotic "depression-like" symptoms may benefit from the addition of antidepressant medication to their ongoing neuroleptic-antiparkinsonian regimen (1). Indications have not been established, however, for the continuation or maintenance use of the adjunctive antidepressant in cases where initial benefit has occurred. We therefore undertook a double-blind study of antidepressant maintenance treatment to help establish clinical guidelines for pharmacotherapy in this circumstance.

METHOD

We studied 10 patients who gave informed consent and who had originally met operationalized qualitative, quantitative, and durational criteria for the postpsychotic depression syndrome (1). These criteria include a diagnosis of schizophrenia or schizoaffective disorder, according to Research Diagnostic Criteria (RDC) (2), for the most recent episode of flagrant psychosis. The criteria also include the presence of a stable syndrome consistent with an RDC diagnosis of major depression (discounting the exclusion based on the previous diagnosis of psychosis) at some point subsequent to the resolution of the psychosis.

All 10 patients had initially experienced a positive therapeutic response to the addition of imipramine to their ongoing fluphenazine decanoate-benztropine regimen (1), and they had remained on this three-medication combination for 6 months. In a double-blind fashion they were then randomly assigned to one of two different treatment groups for the next year. One group of four patients remained on the three-drug regimen unchanged. The other group, six patients, continued to receive the fluphenazine decanoate and benztropine but had their imipramine tapered at a rate of 50 mg/day per week and replaced with matching placebo.

At the beginning of the double-blind trial, at monthly intervals thereafter, or at any point of suspected relapse, patients were rated by using the Clinical Global Impression (CGI) instrument (3) as well as selected items from the Schedule for Affective Disor-

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TABLE 1. Drug Doses of Schizophrenic Patients With Remitted Postpsychotic Depression Whose Adjunctive Imipramine Treatment Was or Was Not Maintained

			Drug Dose					
	Age (years)		Fluphenazine Decanoate (25 mg/ml) (ml/week)		Oral Benztropine Mesylate (mg/day)		Oral Imipramine at Start of Trial (mg/day)	
Group	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Imipramine maintained (N=4)	41.5	16.5	0.71	0.53	4.5	3.0	225	50
Imipramine replaced by placebo (N=6)	33.0	6.3	0.95	0.65	6.3	0.8	225	82
Total (N=10)	36.4	11.5	0.86	0.58	5.6	2.1	225	68

ders and Schizophrenia (SADS) (4). The definition of relapse included development or exacerbation of a depressive syndrome or acute psychotic state, being scored as worse (a score of at least 5) on the global outcome measure of the CGI, and satisfying the treating physician's clinical sense that relapse into a depressive or psychotic state had occurred.

RESULTS

There were no statistically significant clinical or demographic differences between the two treatment groups, as shown in table 1. Half of the patients assigned to each treatment group were men and half were women.

All 10 patients entering the study completed it, either by experiencing a relapse of depression or by not relapsing for 1 year.

All six patients randomly assigned to imipramine discontinuation relapsed into depression-like states. Only one of the four patients maintained on imipramine treatment relapsed into depression. This difference is statistically significant, favoring imipramine maintenance treatment ($p=0.033$, two-tailed Fisher exact test). The mean±SD interval to relapse for patients tapered to placebo was 9.3±5.8 weeks from the initiation of the taper and 5.6±6.0 weeks from the completion of the taper. (One patient relapsed 1 week before the completion of the taper, on a dose of 50 mg/day.) The one patient in the active imipramine group who experienced a relapse did so 44 weeks after the start of the double-blind. The time to study termination (relapse or 1 year without a relapse) was significantly shorter for the patients tapered to placebo ($p=0.013$, two-tailed rank sum test).

Of the six patients in whom depression reoccurred after imipramine discontinuation, three manifested a coincident exacerbation of psychotic symptoms. Their ratings on the SADS items for either severity of hallucinations or severity of delusions increased to a score of at least "moderate." These three patients also each had an increase of at least 2 points in the sum of these hallucination and delusion items over their pretaper rating. The patient who had a depressive relapse while receiving imipramine had no similar increase in psychosis. The mean change in the sum of these two psychosis ratings from the beginning of the double-blind to termination was 0.83 for the patients tapered to placebo and −0.33 for the patients maintained on imipramine treatment. This difference did not achieve statistical significance.

DISCUSSION

These results demonstrate a therapeutic value for maintenance imipramine treatment among at least some patients with histories of syndromally defined postpsychotic depression initially responsive to an antidepressant. It is noteworthy that a rigorous attempt had been made with antiparkinsonian medication to rule out the potentially confounding syndrome of neuroleptic-induced akinesia, which can present a close clinical phenocopy of depression (5). This makes it unlikely that the outcome we observed in the patients given placebo was an emergent akinesia resulting from the withdrawal of an anticholinergic drug, inasmuch as the benztropine, which was continued, is a more potent anticholinergic agent than the discontinued imipramine (6). These double-blind results, therefore, confirm our own earlier open anecdotal experience, which had suggested a therapeutic utility for maintenance adjunctive imipramine treatment in such patients (7, 8).

The mechanism of action of the maintenance antidepressant in these patients is unclear, as are the pathophysiological processes of the postpsychotic depressive state. Speculation about them is beyond the scope of this paper. The pattern of relapse, however, in such a high percentage of patients upon antidepressant tapering after 6 months of continuation treatment (all six patients) is at variance with the typical pattern for patients with primary depression (9).

Caution has often been advised in the literature about the use of antidepressant medication in schizophrenia on the basis of concern that the patients' psychoses might be exacerbated (10). It is therefore of interest that no patients receiving adjunctive imipramine during the course of this trial suffered an increment in psychotic symptomatology. Moreover, three of the six patients tapered to placebo experienced a noticeable flare-up of psychotic symptoms coincident with the reoccurrence of the depressive syndrome. The current series is, of course, too small to draw definitive conclusions, but subsequent to this study, we observed that the psychotic symptoms in each patient resolved along with the depression when adjunctive antidepressant treatment was again added to the neuroleptic and antiparkinsonian medication.

The usefulness of maintenance adjunctive antidepressant treatment in schizophrenia or schizoaffective disorder beyond our tightly defined patient group remains to be explored. However, our results clearly suggest that in cases where an adjunctive antidepressant has been helpful in the treatment of postpsychotic depression, any discontinuation of maintenance antidepressant be done with caution and under close supervision.

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Perceptions of Parental Bonding in Borderline Patients

Joel Paris, M.D., and Hallie Frank, Ph.D.

Eighteen borderline and 29 nonborderline female patients were scored on perceptions of care and of protection by each of their parents. The two groups differed significantly in that borderline patients perceived less care than did nonborderline patients, particularly from their mothers.

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Clinically based theories about the effects of childhood experience on the development of borderline personality disorder have suggested that bonds to parents are characterized either by neglect (1) or overprotection (2). Thus far, the neglect hypothesis is supported by empirical evidence from studies that used family interview data (3), chart review (4), and questionnaires (5–7). In two previous reports from our own clinic (6, 7), recollections of childhood experience by borderline patients suggested a picture of neglect by both parents and did not support an overprotection hypothesis for the development of borderline pathology.

These studies have methodological shortcomings, including the use of instruments that lack validity in measuring childhood recollections (4–7) and the small number of items distinguishing borderline from nonborderline subjects (3). However, the convergence of findings approaching the issue from different methodological perspectives gives the neglect hypothesis sufficient weight to justify further specific testing with a better instrument. The work of Parker et al. (8, 9) on parental bonding provides such an instrument through which scores of childhood recollections can be meaningfully related to a number of adult psychopathological syndromes (9). Parker et al.'s theoretical model is particularly useful because it considers parenting behaviors in terms of care and protection, which were the same dimensions used in our earlier reports.

METHOD

A borderline group and a nonborderline group were drawn from female university students in psychotherapy. Diagnosis was established with the retrospective version of the Diagnostic Interview for Borderline Patients (10). Chart review was carried out on all subjects by a senior psychiatrist (J.P.) who was blind to other measures. Those subjects who obtained a score of 7 or more on the diagnostic interview were included in the borderline group (N=18). Those who received a score of 4 or less were assigned to the nonborderline group (N=29). To ensure that two discrete groups were obtained, patients who received a score of 5 or 6 were excluded from the study. The mean±SD ages for the borderline and the nonborderline groups were 23.0 ±5.48 and 24.0±4.92 years, respectively ($t=-0.67$, $df=45$, n.s.).

To investigate the relationship between borderline psychopathology and perceived parental behaviors, Parker et al.'s Parental Bonding Instrument (8) was administered to all subjects. This is a self-report scale measuring perceptions of two dimensions (care and protection) underlying parental behavior. The care items range from affection to neglect. The protection items range from overprotection to allowance of independence. The scale requires subjects to score their parents on 25 four-point Likert items (12 for care and 13 for protection), on the basis of how they remembered their parents in their first 16 years. Scores for care (range=0–36) and protection (range=0–39) are obtained for each parent. The instrument has been standardized in a series of large-scale normative studies and has reasonable test-retest and split-half reliability (9). Tests for validity of the scale in both normative and clinical populations include concurrence with siblings' ratings of parental behavior, with parental self-ratings, and with clinical ratings drawn from interviews of both subjects and parents (9).

RESULTS

The results are presented in table 1. In order to investigate whether the diagnostic groups differed with respect to scores on the Parental Bonding Instrument, two two-way, mixed-design analyses of variance (ANOVAs) were carried out for both the care and pro-

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TABLE 1. Parental Bonding Scores of Borderline and Nonborderline Female University Students in Psychotherapy

	Score on Parental Bonding Instrument					
	Borderline Patients (N=18)		Nonborderline Patients (N=29)			
Item	Mean	SD	Mean	SD	F or t	df
Care						
Mother	19.17	9.87	25.17	9.73	t=−2.05[a]	45
Father	18.05	8.30	22.45	9.19	t=−1.65[b]	45
Group main effect	—	—	—	—	F=4.67[a]	1, 45
Parent main effect	—	—	—	—	F=1.79	1, 45
Two-way interaction	—	—	—	—	F=0.32	1, 45
Protection						
Mother	16.00	10.11	14.41	7.76	t=−0.61	45
Father	13.61	7.22	14.69	8.23	t=−0.45	45
Group main effect	—	—	—	—	F=0.02	1, 45
Parent main effect	—	—	—	—	F=0.42	1, 45
Two-way interaction	—	—	—	—	F=0.67	1, 45

[a] $p<0.05$.
[b] $p<0.10$.

tection scores, with diagnostic group as the between-subjects factor and parent as the within-subjects factor.

The ANOVA for care yielded a significant main effect for diagnostic group, with borderline patients remembering their parents as being less caring than did nonborderline patients. Neither the main effect of parent nor the interaction term between parent and diagnostic group reached significance. The ANOVA for protection did not yield a significant main effect for either diagnostic group or parent. The interaction term was also nonsignificant.

Planned comparisons of mean care and protection scores between borderline and nonborderline patients for each parent were also carried out. Only the degree of perceived maternal care significantly differentiated the two groups, with mothers of borderline patients reported to have manifested less care. A trend also emerged with respect to paternal care, with fathers of borderline patients perceived as demonstrating less care than fathers of nonborderline patients.

DISCUSSION

The significant main effect on the ANOVA for care showed that the borderline patients perceived their parents as having been less caring than did the nonborderline patients. The results of the planned comparisons showed a significant difference between borderline and nonborderline patients in perceived care from their mothers. Moreover, there was a trend in the same direction that suggested less care from their fathers; that trend would account for the failure of the ANOVA interaction term between parent and diagnostic group to reach significance. These findings tend to confirm our earlier studies (6, 7) and support the hypothesis of biparental failure in the families of borderline patients. Although the role of the mother may be more important, it is possible that the child who becomes borderline is unable to buffer the neglect from the mother with care from the father. As in previous work, we failed to find any evidence of parental overprotectiveness in the recollections of borderline patients.

It could be argued that these findings are the result of falsification of retrospectively reported data. This possibility must be considered in the light of borderline psychopathology, which distorts perceptions of nurturance in current relationships so that mild empathic failures can be seen as neglectful. Alternatively, such perceptions in borderline patients could reflect true neglect by their parents.

While the nature of recollective data makes it uncertain whether true neglect occurred, there are both theoretical and empirical reasons for taking such perceptions seriously. Low levels of parental care would help account for the intense but unstable attachments seen in borderline patients, as well as for dysphoria and impulsivity, phenomena that have been postulated to result from a poor holding environment during childhood (1). Moreover, the hypothesis of neglect as a factor in the development of borderline personality is consistent with empirical evidence.

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Defense Styles Associated With Specific Anxiety Disorders

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The Defense Style Questionnaire was administered to control subjects from the general population (N= 204) and to patients with DSM-III *panic disorder (N=39), agoraphobia (N=39), social phobia (N=23), or obsessive-compulsive disorder (N=18). A specific pattern of defenses was associated with each anxiety disorder.*

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We have recently shown (1) that scores on the Defense Style Questionnaire (2), relabeled in accord with a draft *DSM-III-R* glossary of defense mechanisms (3), can be represented by three factors designated "mature" (sublimation, suppression, etc.), "neurotic" (undoing, reaction formation, etc.), and "immature" (projection, acting out, etc.). A group of psychiatric outpatients, predominantly suffering from *DSM-III* anxiety disorders, scored lower on mature defenses and higher on neurotic and immature defenses than either a normal population control group or a group of family practice patients.

As expected, scores on two vulnerability measures, neuroticism and locus of control, correlated with the level of neurotic symptoms, but they were not different across four anxiety disorders: panic disorder, agoraphobia, social phobia, and obsessive-compulsive disorder. Defense factor scores did vary across these diagnostic groups. We examined a subsample of these patients to explore the extent to which individual defense mechanisms are associated with these four diagnoses.

METHOD

The subjects for this study were 204 control subjects from the general population (1) and 119 patients accepted for behavioral treatment of *DSM-III* anxiety disorders. The mean±SD ages of the control group (92 men and 112 women) and the patient group (35 men and 84 women) were 37±13 and 36±11 years, respectively. There were 39 patients with panic disorder, 39 with agoraphobia, 23 with social phobia, and 18 with obsessive-compulsive disorder. Patients with concurrent drug or alcohol problems or with major affective disorders were excluded. The diagnoses of all but six patients were made clinically by one of us (G.A.). These diagnoses were confirmed by an independent clinician using the Diagnostic Interview Schedule who had not seen the patients previously. Six patients with obsessive-compulsive disorder were under the care of other senior psychiatrists, who remained responsible for the diagnoses. All patients completed the Defense Style Questionnaire (1).

There were two major questions: Were the defense patterns of patients with particular diagnoses different from those of the general population? and Could these patterns of defense differentiate between diagnoses? The standardized deviation (effect size) between each patient group and the population control group was calculated for each defense on the basis of scores on the Defense Style Questionnaire. Profile and discriminant analyses of the relationship between each patient group and the control group and between each pair of diagnostic groups were then conducted.

RESULTS

In table 1 we present the deviation, in effect size units, of each patient group's mean score on each defense from the score of the control group. The level of significance was computed from a two-tailed t test with $p<0.05/20$ (Bonferroni correction).

Clinicians will find table 1 of interest. Compared to the population control group, the patients with panic disorder were more likely to endorse displacement, and patients with agoraphobia were more likely to endorse somatization, displacement, reaction formation, and idealization. The patients with social phobia were more likely than the control subjects to endorse displacement and devaluation and less likely to endorse humor as a defense. The patients with obsessive-compulsive disorder were less likely than the control subjects to endorse humor but more likely to endorse undoing, projection, and acting out as preferred defenses.

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TABLE 1. Differences, in Effect Size Units, of Scores on the Defense Style Questionnaire Between 119 Patients With Anxiety Disorder Diagnoses and 204 Population Control Subjects

	Difference From Control Group, in Effect Size Units					
Defense	Panic Disorder (N=39)	Agoraphobia (N=39)	Panic and Agoraphobia (N=78)	Social Phobia (N=23)	Obsessive-Compulsive Disorder (N=18)	All Anxiety Patients (N=119)
Mature defenses						
Anticipation	−0.10	−0.26	−0.18	−0.25	−0.05	−0.17
Humor	−0.25	−0.50	−0.38	−0.66[a]	−1.22[a]	−0.56[a]
Suppression	−0.33	−0.25	−0.29	−0.50	−0.42	−0.35[a]
Sublimation	−0.03	−0.36	−0.19	−0.64	−0.32	−0.30
Neurotic defenses						
Pseudo-altruism	0.08	0.35	0.22	−0.28	0.29	0.13
Idealization	0.22	0.48[a]	0.35	0.00	0.58	0.32
Reaction formation	0.29	0.58[a]	0.44[a]	0.47	0.60	0.47[a]
Undoing	0.43	0.29	0.36	0.50	1.20[a]	0.51[a]
Immature defenses						
Acting out	0.08	0.11	0.09	0.29	0.79[a]	0.24
Denial	0.02	0.00	0.01	−0.41	−0.05	−0.08
Devaluation	0.08	0.29	0.19	1.07[a]	0.88	0.46[a]
Displacement	0.84[a]	0.78[a]	0.81[a]	1.31[a]	0.31	0.83[a]
Dissociation	0.22	0.47	0.35	0.44	−0.02	0.31
Autistic fantasy	−0.25	−0.24	−0.24	0.11	0.17	−0.11
Isolation	0.18	0.04	0.11	−0.04	0.58	0.15
Passive aggression	0.38	0.16	0.27	0.53	0.55	0.36[a]
Projection	0.23	0.40	0.32	0.51	0.95[a]	0.45[a]
Rationalization	0.23	0.04	0.13	0.12	0.38	0.17
Somatization	0.30	0.86[a]	0.58[a]	0.75	0.62	0.62[a]
Splitting	0.16	−0.28	−0.06	0.31	0.08	0.03

[a] Difference is significant at $p<0.05/20$ (i.e., includes Bonferroni correction), according to two-tailed t test.

The pattern of endorsement of defenses associated with each diagnosis was then compared with a profile and a discriminant function analysis run according to the SPSS-X MANOVA procedure (4, 5). As panic disorder and agoraphobia are considered one disorder in *DSM-III-R*, we first compared these two *DSM-III* disorders. The defense styles of these two groups of patients were not significantly different according to a test of the parallelism of the profiles (Pillai (P): F=1.18, df=19, 58, p=0.31) and discriminant analysis (Pillai (D): F=1.30, df=20, 57, p=0.22). We therefore combined these groups and compared the three remaining groups—panic/agoraphobia, social phobia, and obsessive-compulsive disorder—with the same statistic. According to both tests, the profile of defenses for panic/agoraphobia was different from those for social phobia (Pillai (P): F=2.71, df=19, 81, p=0.001; Pillai (D): F=2.55, df=20, 80, p=0.002) and obsessive-compulsive disorder (Pillai (P): F=2.53, df=19, 76, p=0.002; Pillai (D): F=2.38, df=20, 75, p=0.004). The profile of defenses in social phobia was only marginally different from the pattern in obsessive-compulsive disorder (Pillai (P): F=2.21, df=19, 21, p=0.04; Pillai (D): F=2.10, df=20, 20, p=0.05).

DISCUSSION

Anna Freud (6) stated that neurotic symptoms are a consequence of the "unvarying use of a special form of defense, when confronted with a particular instinctual demand." Yet the empirical measurement of defenses has proven difficult. Vaillant (7), using a time-consuming rating of interview material, illustrated the relation between maturity of defenses and a history of psychological illness. Bond developed a questionnaire for the experimental study of defense mechanisms, and he and others (8–10) demonstrated that the results of this questionnaire covaried with measures of ego maturity and patient status, but they found no systematic association between patterns of defenses and particular diagnoses.

We have relabeled a version of that questionnaire to be consistent with the definitions in "A Draft Glossary of Defense Mechanisms for *DSM-III(R)*" (1–3) and have shown that the level of defense maturity, as judged from factor scores, varies with diagnosis. In this paper we report evidence that the clinically observed relation between individual defenses and diagnosis is supported by the profile of Defense Style Questionnaire scores: patients with panic disorder (with or without agoraphobia) use displacement, somatization, and reaction formation; patients with social phobia do not use humor and do use devaluation and displacement; and patients with obsessive disorder do not use humor but use undoing, acting out, and projection as preferred defenses. It would be desirable for these findings to be replicated to confirm their reliability, especially in view of the small sample size of some of the diagnostic groups. The new scale has also to be validated against a proven interview method, but these results lend some support to the construct validity of the instrument, particularly as the pattern of defenses did, in these samples, discriminate between the different diagnostic groups.

The clinical value of the instrument is its ability to aid in diagnosis and illuminate difficult transactions between patient and therapist. In psychotherapy research it should be considered as a psychodynamically coherent measure of outcome that is relatively independent of symptoms.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

FAMILIES AND FAMILY THERAPY

Family Evaluation, *by Michael E. Kerr and Murray Bowen. New York, W.W. Norton & Co., 1988, 380 pp., $29.95.*

Count Tolstoy claimed that unhappy families are all different. Miss Manners says they are all alike. Drs. Kerr and Bowen are somewhere in between. To them, unhappy families are undifferentiated.

Bowen's family systems theory consists of eight basic concepts: differentiation, triangles, family projection, multigenerational transmission, sibling position, emotional cutoff, nuclear family process, and societal emotional process. This book studies each concept in detail. But make no mistake about it. For Kerr and Bowen, differentiation is the universal joint around which all psychopathology revolves. Their application of family systems theory consists of a scale of differentiation from 0 to 100 on which the maturity of individuals can be measured. Total lack of differentiation rates 0; complete differentiation rates 100. This attempt at quantification of development is also related to psychopathology. For example, a person rated 0–10 on the differentiation scale is said to lack emotional boundaries between self and others. So far so good. But the overemphasis on this notion of differentiation is a flaw. There is a great deal more to human development than the dimensions of dependence and independence. Some cultures value more autonomy and differentiation than others. And the concept of differentiation-separateness is not adequate to explain attachment-connectedness. The latter does not simply happen in the presence of more of the former. It has a life of its own. Indeed, the quest for more differentiation and more autonomy at times resembles the diet faddist seeking higher levels of "good" cholesterol for better, better, and better health.

The major portion of this book was written by Michael Kerr; the epilogue was written by Murray Bowen. Each wrote his part independently of the other (perhaps the ultimate illustration of differentiation). The purpose of Kerr's chapters is to develop Bowen's paradigm of the 1950s into a model for practice in the 1980s. They are well done. Kerr's scholarly sociobiological review moves toward a unifying theory of behavior. His clinical illustrations are sensitive and practical. His chapter on triangles is a clear presentation of this concept, with illustrative diagrams that are more than billiard balls bouncing off one another. His final chapter, on family evaluation, funnels years of experience into a comprehensive system of family assessment. This chapter will be of considerable use to clinicians and trainees.

Bowen's epilogue consists of the bittersweet reflections of one of the pioneers in the field of family therapy (but without reference to other pioneers in the field). It is a history of the family therapy movement, a fascinating odyssey described by one of the great explorers. But it also illustrates how far the field has *not* come. The early antidiagnostic years of family therapy slowed the development of objective criteria for family assessment. Until family diagnosis catches up with family therapy, it is unlikely that there will be a dimensional axis to psychiatry's *DSM,* whether *IV* or *V.* But Drs. Kerr and Bowen have made a worthy move toward this goal. Their book should be passed around and read by all those who work in the field of family relationships.

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Handbook of Behavioral Family Therapy, *edited by Ian R.H. Falloon, M.D. New York, Guilford Press, 1988, 460 pp., $39.50.*

Until recently, few would have mentioned behaviorism and family therapy in the same breath. In some ways, it is a natural relationship, if not a marriage. Family therapies, more than most psychosocial therapies, have primarily focused on observable behaviors. Behavioral therapies are most effective when carried out in a structured setting, and the family is such a setting. Even so, there are likely to be purists in either camp who may be offended by this juxtaposition. We are not among them. This book brings together the empirical tradition of behaviorism and the rich clinical tradition of family therapy in a manner congruent with a growing tendency toward eclecticism in psychotherapy. This tendency lowers the barriers between schools of psychotherapy and defines "what is common among them and what is useful in each of them" (1). This volume, although clearly of a behavioral orientation, will be of value to all who are interested in the psychosocial therapies. Its descriptions of other schools of family therapy, although framed in learning theory, are fair and accurate.

Handbook of Behavioral Family Therapy, edited by one of the leading figures in this newly defined field, is divided into two sections. The first considers general, conceptual, and historical issues, and the second deals with the application of behavioral family therapy to specific patient populations. In sum, the book delivers considerably more than its title promises. It lives up to its handbook label in that it is clear, concise, and instructive. It goes farther than similar books by offering insights into why certain techniques might be helpful and by referencing data wherever possible. The 32 contributors (including seven physicians) do not limit themselves to classical learning theory or behavioral interventions. In many instances in this volume, behavioral means "empirically supported."

The strength of the general section lies in the description of the evolution of the field of behavioral family therapy. This field began with "the involvement of parents in the modification of the disturbed behavior of their children" (p. 3). Gradually, such interventions developed sophistication. They shifted from an analysis of individual child behaviors to a consideration of coercive parental practices to analyses based on reciprocal interactions. The authors emphasize behavioral family therapy's differentiation by considering clinical issues beyond the problems of parent and child. Cognitive perspectives, contextual assessments, and the evaluation of circular reinforcement patterns in couples and families are all part of a behavioral family assessment. The concern of such assessments is not only with an increase or decrease in positive statements but also with the sequence and meaning of verbal messages. This perspective is similar to circular questioning described by systems-oriented family therapists. This section closes with a concise, psychodynamically accurate chapter on resistance to change. Its inclusion is evidence that behaviorism, long proud of brief treatments, now acknowledges the pervasive, persistent nature of many types of psychopathology that require more persistent, longer treatments.

The 12 chapters in part two, Specific Applications, are somewhat uneven in quality of literature reviews, clinical descriptions, and intervention protocols. Some chapters are laudable for their simultaneous behavioral emphasis and description of the role of behavioral family therapy when used with other therapies. Chapters on anxiety disorders and obsessive-compulsive disorders emphasize that unsuccessful behavioral interventions often reveal pervasive, persistent maladaptive thoughts and feelings. Such characterological postures may require other types of psychotherapeutic or pharmacological intervention. This breadth, consistent with biopsychosocial psychiatry, makes these chapters valuable teaching aids in psychiatric residency training programs. Dynamically oriented clinicians will see other chapters, such as the one on depressive disorders, as offering less scope and as somewhat trivial. In fairness, this unevenness is not just an issue in writing or editing style but also reflects the status of the field. However, regarding actual subject matter, it is hard to understand why eating disorders are neglected while the greater part of three chapters are given over to schizophrenia.

In addition to its substantive contributions, we believe that this book's approach to two perennially controversial areas deserves further comment. Several contributors discuss the relationship of behaviorism to dynamic therapies and the relative contributions of biological and psychological vulnerabilities to the etiology of clinical disorders. In both these areas, we experienced this volume as a bridge for the field.

Psychodynamically oriented clinicians will be pleasantly surprised by the inclusion of material dealing with countertransference, resistance, and intrapsychic conflict. The initial chapter describes early behavioral interventions with families as simplistic in that they tried to eliminate behaviors "without pinpointing any of the conflictual attitudes or feelings that contributed to the overt behavioral problems." Later on we read that the aim of an interpretation is "to move the couple toward recognition and discussion of otherwise obstructive, underlying, unspoken issues or feelings." Similarly, the more recent family therapy literature cited indicates that therapists with a dynamic bent do indeed use behavioral concepts, such as social skills remediation, education, and support (2). Such pluralism may confuse the beginning psychotherapist but benefits the field generally and our patients specifically.

Several chapters deal with major psychiatric disturbances. The book's approach is biopsychosocial—there are many variables contributing to the onset of mental disorders. Within the book, emphases vary. Some authors say there is no evidence that family interaction causes schizophrenia but that families are responding to illness, a popular idea these days. Other authors cite studies of the serious disturbances of children that describe parents' psychological problems leading to misperceptions of their children's behavior. In such instances, families contribute to the onset of illness, currently not a popular idea. One author describes psychosocial vulnerabilities to most major mental disorders occurring through the mechanisms of "socioenvironmental stress" (family conflict, for example) and "lack of protective factors" (interpersonal competence, for example).

This tension is a desirable facet of the book because it reflects our current understanding of the relationship between family functioning and psychiatric disorders. The representation of both points of view helps temper a growing biological reductionism in the field. Yes, families can have a member biologically vulnerable to a certain disorder. They can also engage in interactions that compromise members' adaptive capacities and that have a life of their own apart from being a response to illness. Totally implicating mothers or genes as culpable etiological agents is not good biopsychosocial psychiatry.

We believe that this book will find an important place in the psychiatric literature. It is particularly timely as psychiatry returns to medicine. Its emphasis on empiricism and its conservative approach to the role of the family in the onset, evolution, and maintenance of psychiatric disorders will facilitate this return. This book will also place family therapy in a scientific context. Family therapists have often had little impact in medical settings. Their conviction that family processes cannot be measured and their lack of attention to individual contributions to disorders, both biological and psychological, are two reasons. Behavioral family therapy addresses these deficiencies.

The book's innovative reframing of behavior therapy and family therapy constructs will be of most use to the seasoned clinician. Beginning psychotherapists will find this a valuable resource to consult. It is an effective blend of pragmatic strategies and conceptual background. It truly expands the limits of behavior therapy and family therapy. It is for all who study, and work with, the change process.

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Rituals in Families and Family Therapy, *edited by Evan Imber-Black, Janine Roberts, and Richard A. Whiting. New York, W.W. Norton & Co., 1988, 414 pp., $34.95.*

What do rituals have to do with psychotherapy? If we are interested in helping patients change, we should be interested in the usual and culturally sanctioned ways that human beings have devised to change their lives and to commemorate and thus to define that change; rituals are such inventions. Furthermore, the concept of ritual can lead us to think about the theories of psychotherapy, since ritual draws our attention to the symbolic nature and meaning of therapy—its humanistic origins rather than its objective, fact-finding, and scientific roots.

The authors define rituals in this book to include 1) the family and the therapist together deciding on the plan, which will include content, form, and occasion, 2) determining much of the plan in advance but permitting opportunity for change, and 3) reliance on symbols and symbolic action. The goal is to help the family or couple find a way of experiencing and/or celebrating a change that will have an impact at cognitive, behavioral, and affective levels. Examples of rituals are having a couple list separately their grievances, discuss these, and then burn them; a house-cooling party for a divorced woman to define her new status; and getting rid of the symbols of former behavior while still retaining them, as in freezing a pair of kid gloves in an ice tray to symbolize that one is giving up treating a child this way but still has access to the behavior.

This book is good, and I am glad I read it. It will be useful to family and couples therapists and, indeed, to innovative individual therapists. Unfortunately, *Rituals* suffers from an all too common editorial failure. From inside this large and bloated book an excellent smaller book is struggling to emerge, one in which the editors' own exemplary chapters would be featured. There are chapters describing the use of rituals in far too many specific populations. To list but a few, these include couples, children, adoptive children, alcoholic families (a particularly good chapter), and women but not men. The reader bogs down in a book that, clearly, is not intended to be read as a whole. On the other hand, the reader looking for a ritual for a particular family will not find it in this book. Indeed, the authors themselves would decry the notion that a handbook of rituals could be written.

Increasingly, psychotherapists have attempted to integrate psychodynamic and behavioral methods. The problem for family therapists is that the rather simpler symptoms that traditional behavior therapists treat are quite different from the complex interactional behaviors of symptomatic families. So family therapists have devised a large number of ways of making these interactive symptoms visible and modifying them. Among the ways of making family behaviors more visible are using family photographs, taking members of the family behind a one-way screen to observe the rest of the family, and having the family view videotapes of themselves or other family sessions. However, making an interaction manifest is often insufficient to enable the family to change. In these instances, the therapist must find ways of intervening more directly; these interventions are usually subsumed under the heading of "tasks." They can occur within the session—for example, altering family sitting arrangements and assigning who may talk with whom—or may involve the prescription of "homework" to be done outside the session. Sometimes the task involves prescribing the symptom or is based on the family's oppositional tendencies or is counterintuitive and may be labeled "paradoxical."

From this perspective, the use of rituals in therapy can be seen as an effort to influence dysfunctional family interactions using interventions that involve the integration of cognition, behavior, and affect into a single gestalt—the ritual. One hopes that the enactment of a well-designed therapeutic ritual with its focus and symbolic nature will have substantial therapeutic impact. This book can be useful to therapists seeking to broaden the ways in which they help their patients and makes a valuable contribution to the humanistic traditions of psychotherapy.

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Family Games: General Models of Psychotic Processes in the Family, *by Mara Selvini Palazzoli, Stefano Cirollo, Matteo Selvini, and Anna Maria Sorrentino; translated from the Italian by Veronica Kleiber. New York, W.W. Norton & Co., 1989, 285 pp., $27.95.*

In the spring of 1986 while on sabbatical in Verona, I was interested in meeting and observing the work of Mara Selvini Palazzoli, the well-known Italian family therapist. My interest was piqued both by her enthusiastic, almost fanatical following among some family clinicians and by her rather critical and chilly reception by distinguished researchers in the United States. After being told that I could bring none of my Italian colleagues because it would interfere with "the research," I attended a session conducted by Dr. Palazzoli and discussed the case with her and her colleagues at lunch afterward. It was clear that what she calls research (and refers to in the book as research) means observation and discussion of cases, not state-of-the-art scientific study of psychotherapy process and outcome.

This book is described as detailing the work since the late 1970s, when Dr. Palazzoli "abandoned" as "unsatisfactory" the techniques of using paradox and the invariant prescriptions. Some flavor of the book (and its level of discourse) can be gleaned from the authors' 1) aim: "How are we to link a parental couple's malfunctioning with that of their child?" (p. xiv), 2) intent: "to seek out the roots of what is commonly spoken of as mental illness" (p. xiv), and 3) sample: 290 cases seen in their clinic from 1979 to 1987, ranging from "stuttering to schizophrenia to trichotillomania," of which about one-half were diagnosed as having autism (45 patients) or anorexia nervosa (93 patients) (from the only table in the book, on p. xvii). The authors also comment early in the book that their work cannot be termed scientific (p. xv). But if it is not science, what is it?

The contents of the book detail what the authors call "their original prescription," and "the new prescription." They stress the point that their new ideas go beyond psychoanalysis and systems theory, but I do not see any extension of modern integrative versions of both of these models as I understand them. Their new techniques refer to family "games," i.e., recurring phenomena that are not under family members' control and that presumably drive them to psychotic behavior:

> Game, to us, is a metaphor and as such will forever remain intuitive and elusive. We have quite another purpose in mind, namely to come ever closer to defining exactly the processes that lead to a subject's psychotic behavior. To this end we are attempting to devise *models* of the psychotic *processes* that develop in a family. (p. 151)

The ideas in the book are clearly at substantial variance with current models that view schizophrenia as a complex disorder with biological, psychological, and social factors influencing cause and course—a disorder requiring treatment with both somatic and psychosocial-psychoeducational interventions. Of note, the word "medication" does not appear in the index.

I found the writing (or translation) often turgid; for example:

> Our work with the invariant set of prescriptions enabled us to draw up a repertoire of strategies we could use to counteract the indictment of the parents that our

> basic hypothesis about the onset of psychosis inevitably entailed. (p. 238)

The authors also develop straw men by attributing, out of context, a simplistic version of other researchers' theories, as in the following example:

> Anderson, Hogarty, and Reiss (1980), for instance, acquit the parents on the reassuring grounds that schizophrenia is a biological disturbance and the parents' task, therefore, is merely to take good care of the patient and avoid any stressful factors that may bring on a relapse. (p. 238)

The authors then somewhat gratuitously assert how their methods are much better:

> [In our treatment context, family members] feel properly appreciated and can be enlisted in collaborating actively in a process designed to bring about change. In this sense, then, appointing the parents as co-therapists is an eventful move. (p. 238)

As I have noted, this book does not speak in the language of science, use scientific methods, or present data. As such, the conclusions and claims of efficacy made in the volume and, for that matter, my evaluation of the work are moot. In fact, only data will tell whether the authors' formulations, or some other, are helpful or injurious over the long haul to patients and their families. (Families commonly perceive such system formulations as blaming them for their children's psychoses.)

On the other hand, this clinical team is consistently striving to understand what they are doing. And they do think innovatively—albeit within their own sphere. This book will make interesting reading for those who are partial to the work of the Nuevo Centro per lo Studio della Famiglia in Milan.

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Ethical Issues in Family Therapy, *edited by Sue Walrond-Skinner and David Watson. New York, Routledge & Kegan Paul, 1987, 163 pp., $49.95; $15.95 (paper).*

Just when we thought the new conservativism had established a strong foothold in the world, the British remind us that there are such things as ethical issues, even in family therapy. This little text, edited by a family therapist and a philosopher, presents essays by 10 different writers who offer perspectives on family therapy from their own backgrounds in social work, psychology, philosophy, or psychiatry.

When I first agreed to review a book on ethical issues in family therapy, I envisioned reading about such things as privileged communication, record keeping, and informed consent. Instead, I discovered that there is a school of anti-systemic family therapy out there. This book aims at the very roots of systemic therapy, striking most vehemently at strategic techniques.

Perhaps the most philosophically based argument against family therapy has to do with causality. In separate chapters, David Watson and Adam Morton both argue that the belief in the circularity of causal patterns within families leads to a dismissal of, or at least a tendency to ignore, the moral responsibility of every individual for the actions he or she chooses. In a similar line of reasoning, the essays by Watson and by Andy Treacher emphasize the barrier that is erected between the strategic therapist and the patient when one fails to consider an individual's conscious intent for a given behavior. Accordingly, this emotional barrier is associated with the therapist's attitude that families must be treated as dangerous adversaries who need to be tricked into change. Treacher seems to think that the therapist's choice of strategic techniques tells us more about the therapist's interpersonal anxieties and desire for power than about the family's dysfunction.

Two essays emphasize the place of the family within a larger social context, a perspective that their authors were surprised to find had been largely ignored by systems theorists. Sue Walrond-Skinner discusses the feminist view, which considers most therapy with women to be an effort to perpetuate society's patriarchal traditions and to keep women in a dependent status. She suggests that therapists would do well to confront their own sexism and to keep societal pressures in mind when counseling women, whether individually or in families. Philip Kingston puts the family within a larger social framework, suggesting that some problems of individual families may best be tackled at the community or governmental level.

Most of the authors seem to have put all forms of family therapy in the same, rotten barrel. Two authors, John Carpenter and Andy Treacher, concede that it is strategic therapy which is on the most shaky ethical ground. Structural therapy, they admit, offers the therapist much more freedom to engage in an honest relationship with families.

Despite the incorrigible British habit of using words like "whilst" and "amongst," this little text presents much valuable food for thought for all therapists hungry for a more certain ethical base in their work. This is important in a discipline that has put so little emphasis on ethical, or even legal, issues. All readers are sure to find something to which to object within its pages, but even this is a worthwhile exercise in challenging, and perhaps confirming, one's established beliefs.

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PSYCHOSOCIAL ISSUES

Fugitives of Incest: A Perspective From Psychoanalysis and Groups, *by Ramon C. Ganzarain, M.D., and Bonnie J. Buchele, Ph.D. Madison, Conn., International Universities Press, 1988, 113 pp., $25.00.*

In the past decade, the mental health professions have rediscovered the reality of incest. We no longer discredit our patients' reports of childhood abuse or, worse, attribute these reports to fantasy or desire. We have learned to ask and to listen. As a result, we have learned that many psychiatric patients have extensive histories of incest.

But getting the history is only the beginning. Once we've got it, what do we do with it? How does the knowledge of a history of early abuse inform psychotherapy? What changes in technique, what additional modalities of treatment might be useful? By now, many clinicians have realized that group treatment can be especially valuable for survivors of many sorts of trauma, including incest. But what sorts of groups?

Lots of clinicians are out there flying by the seat of their pants. We are at the point in this field where detailed reporting of innovative treatment methods is sorely needed.

Here are two experienced clinicians who have run a long-term psychotherapy group for incest survivors, who have treated some 25 patients in the course of several years. This book could have been so timely and so useful. Unfortunately, it tells us almost nothing about what the authors actually did. How were the patients selected and why? How did they fare in the group? Was any attempt made to document the outcome of group treatment? Can we learn anything from this book about what sort of patient does well or badly in this sort of group? Sadly, the answers are no. The authors' observations are masked by a thick layer of metapsychological language that makes it impossible to replicate their work.

Moreover, the authors do not seem to be aware that there are important theoretical and technical questions about group treatment for this population, questions that need to be addressed explicitly. For example, they describe a co-leadership model pairing a senior male psychiatrist and a more junior female psychologist but say nothing about the power dynamics implicit in such an arrangement. They seem oblivious to the impact such a model might have on sexually victimized women.

The best parts of the book are the case vignettes and the discussion of the therapists' countertransference. Here the authors make it clear that they have a sensitive understanding of many complex psychodynamic issues that emerge in treatment of incest survivors. But we already have more comprehensive books that address these issues (1–4). I hope that someday these authors will write another book about their group and tell us what actually happened.

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Abuse and Victimization Across the Life Span, *edited by Martha B. Straus. Baltimore, Johns Hopkins University Press, 1988, 270 pp., $36.00.*

This unpretentious, modest-looking book answers many questions that physicians, health workers, advocates, lawyers, policy makers, and legislators may have about child abuse, a thorny and complex issue of growing importance in our modern culture.

Abuse of children seems most often to be the reason why agencies and their representatives are called on to render assistance and to help in prosecuting those who have taken advantage of the very young and the very vulnerable. Abuse, at times, seems to have an age selectivity for children, and quite often we tend to give higher priorities to those examples of abuse than to abuse involving husbands raping their wives or of caretakers and relatives abusing the elderly.

Martha B. Straus, in order to broaden the often unwarranted narrowness of the field of victimization and abuse, assembles a faculty of 17 contributors for a book that is destined, in my opinion, to become some sort of classic, at least until something better is written in this field.

In this book abuse and victimization are studied—as stated in the title—across the life span. The abuse of children is scrutinized from the very beginning of life and as it proceeds through childhood and adolescence and on through the life process.

In addition, recognizing that this field of study is not confined to an understanding of the abuser and the abused, the authors pay attention to what they call special topics in the final and fourth chapter of the book.

The book is organized along a progressive continuum that renders the data accessible and the material rather readable. Along the lines of progression, the authors intersperse clinical case histories that illustrate the points they wish to make. The progression through the chapters and the different contributions proceeds very smoothly with little or no redundancy among the authors.

What emerges, then, is a conspicuously readable, interesting, and well-written account of the field of abuse and victimization with emphasis on specific problems as they develop according to a developmental grid.

This book would be of assistance to those psychiatrists who are asked to render opinions on issues concerning abuse and neglect and for those child psychiatrists who often are required to be experts in this field. It will also be useful to anyone dealing with abuse and victimization in a society where such behaviors are no longer unusual.

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Doctors' Marriages: A Look at the Problems and Their Solutions, *by Michael F. Myers, M.D. New York, Plenum, 1988, 225 pp., $29.50.*

Dr. Myers, a psychiatrist specializing in marital therapy, recounts his experience with 130 couples and 75 individuals who consulted him because of marital problems. In this book he considers marital problems in general and focuses on those which characterize doctors' marriages. He addresses physicians whose marriages are troubled and hopes that their therapists will also find the book helpful. The book is organized into chapters that consider problems at different stages in the careers of physicians and indicate the varied problems with which doctors contend.

The conflicts in the marriages of medical students center around the alienation and loneliness of spouses because of the pressure of the physician's work, financial worries, academic difficulties, and unexpected pregnancy. In addition to the continued demands of work and the separation it entails, the marriages of residents are strained by the need to consolidate professional attitudes, assume responsibility, and make decisions about future location.

The marital problems of male physicians center around difficulty in communication, drug and alcohol abuse, and psychiatric problems. In general, men do not communicate as freely as women. They hide their feelings and are reluctant to ask for help.

Women physicians struggle with feelings of guilt related to failure to live up to their perfectionist ideals. While striving to achieve professionally, they are concerned that they may be considered unwomanly because of their departure from the stereotypical female role. The tensions generated when women are more successful than their husbands can strain a marriage.

In addition to the usual tensions already mentioned, Dr. Myers discusses unusual and critical situations in marriage. The sources of stress in gay and lesbian "marriages" are similar to those in all intimate relationships and are exacerbated by the prejudice against homosexuality. Physicians are particularly vulnerable to prejudice because it may affect their referrals. Divorce, remarriage, and illness of self, children, or spouse represent stresses for physicians as they do for anyone else.

In addition to vignettes presented throughout the book to illustrate his approach to the problems he presents, Dr. Myers devotes a chapter to treatment. His stated biopsychosocial orientation results in a comprehensive account of his patients' problems and their resolution. He notes his limitations and failures and is aware that some of the solutions he offers are simplistic and overly optimistic.

This book will be useful to physicians with marital problems and to those who treat them, provided the physician-patient is not encumbered by serious psychopathology.

REBECCA Z. SOLOMON, M.D.
Hartford, Conn.

Deceptive Distinctions: Sex, Gender, and the Social Order, *by Cynthia Fuchs Epstein. New Haven, Conn., Yale University Press, 1988, 300 pp., $25.00.*

Past explanations of differences in the accomplishments of men and women have assumed that inherent biological factors accounted for disparities. More recent research has challenged this view and suggested a more complex interaction between biological and psychosocial phenomena. In this book, Epstein argues that men and women share an overlapping range of capabilities and that most distinctions are societally induced. In noting that all societies provide some, usually biological, explanations for observed gender differences, she iterates Stephen Jay Gould's warning that the problem is how to distinguish between biological determinism—a theory of limits—and a biological view that incorporates potentiality—a range of capabilities.

Epstein indicates that the data available in the area of gender similarities and differences are generally poor, especially in terms of empirical confirmation. She emphasizes two arguments that have been cited in more recent discussions of this subject: 1) it is difficult for members of a social order to question their own order and 2) the structure of the social order fosters specific kinds of thinking and knowing. Since gender distinctions are a basic element in the creation of a social order, and since distinctions tend to be stratified with men at higher rank, it is inevitable, she believes, that men have a stake in justifying and continuing the status quo.

In her discussion of the research, Epstein attends to recent critiques of the methodology of scientific analysis of sex and gender, and she carefully reviews an enormous body of investigation from various disciplines. From the sociobiological perspective, she indicates that differences are recorded but little is delineated regarding their meaning or how species-specific extrapolations can or should be made. Shifting from this focus, she enters the world of personality and focuses on emerging work on the psychology of men and women as well as intrapsychic determinants of behavior. Here her psychoanalytic critique is both brief and somewhat dated, limiting its contribution to her argument.

Her greatest strength is in the delineation of gender in the social system—her emphasis on the sociological perspective. Most of the book is occupied with a detailed and exhaustive presentation and analysis that include social systems, social control, the structure of work, the political process, and the family.

Epstein concludes by indicating that dichotomous thinking is pervasive in our lives and contributes to our concepts of roles and behaviors. She believes that differences are often overemphasized and manipulated and can be a cause of inequality. In this sophisticated and incisive critique, Epstein ranges from sociobiology to linguistics and from politics to psychiatry to iterate her position that gender differences are often used to support the existing structure rather than to advance our understanding or expand our horizons.

CAROL C. NADELSON, M.D.
Boston, Mass.

Modern Perspectives in Psychosocial Pathology, *edited by John G. Howells, M.D. New York, Brunner/Mazel, 1988, 358 pp., $40.00.*

In his preface, the editor presents an enticing idea. Here will be a book that "focuses on how psychopathology in individuals and families impinges on society, creating social psychopathology, or arises in society itself as a social group expression of psychopathology." At times the editor's goals are achieved, but, for various reasons, there are other occasions when the book falls short.

The progress in psychiatry during the last two decades has been remarkable in ways that we are still becoming accustomed to. We remain more likely to conceptualize psychiatric dysfunctions using a compartmentalized approach than we are to use an approach that views dysfunctions as phenomena occurring in a system of interacting elements. Thus, we must ask if the editor is making a useful distinction by applying the term "social psychopathology." We could answer that question if the book provided a coherent explanation of what constitutes social psychopathology. When one considers that individual psychopathology takes place on a biological substrate, impinges on society, and is impinged upon by society, social psychopathology may not be so easy to define. The book does not adequately address this question, and the selection of many of the chapters seems arbitrary. Nevertheless, some psychiatric disorders have a greater impact on society than others and some disorders seem to be directed against society or at least transgress social values. When the book stays within the boundaries of transgression and disintegration, it provides some interesting reading.

Beginning with problems centering on children, there are particularly well-written chapters on child abuse, child molesters, incest victims and their families, and childhood fire setting. These chapters will provide an excellent introduction for those who want to know more about such things. The editor's goal is closest to being achieved here. The chapter on aggression in the classroom is culture bound, dealing with the bully in Great Britain.

The middle section of the book addresses what the editor refers to as social pathology in adults. Chapters on alcohol abuse, pathological gambling, homicide, Munchausen syndrome, agoraphobia, and social phobia are included. Again, the chapters are generally well-done, accurate, brief reviews of the topics. However, there is little here that could not easily be found in other sources, often by the same authors. There is nothing inherently wrong with this gathering of papers, but they are not part of a coherent theme. Why should agoraphobia and social phobia be included and obsessive-compulsive disorder or, for that matter, the personality disorders or schizophrenia be left out?

The final section includes chapters on the homeless mentally ill, the dual-career family, unemployment, work dysfunction, personal disaster, cults, terrorism, and social disaster. The same comments made about the middle section of the book apply here.

Some of the chapters seem to represent the individual authors' particular points of view, and there is little attempt made to link the chapters together. These chapters often comment on salient dilemmas but not in ways that necessarily enlighten us with regard to clinical problems.

In summary, this volume contains a series of introductory chapters on a variety of psychiatric and social topics. The usefulness of the book will depend on whether the selection of topics meets a given reader's needs.

ARNOLD WERNER, M.D.
East Lansing, Mich.

DISORDERS IN CHILDREN

Assessment and Diagnosis in Child Psychopathology, *edited by Michael Rutter, A. Hussain Tuma, and Irma S. Lann. New York, Guilford Press, 1987, 477 pp., $35.00.*

It is not surprising that this team of editors has produced an outstanding book, but it is amazing that Rutter has again placed his mark on another heavyweight classic. Unlike his other monuments, this one is merely the size of a book. It can be read in multiple sittings and is right on the money for any psychiatrist interested in partaking of the new age of scientific description of adolescents and children. For the many clinicians and researchers who want to use the new quantitative or structured instruments, this is the book.

Written in *DSM-III* days, it contains a full awareness and detailed knowledge of the changes in *DSM-III-R* and *ICD-10,* which include data-based revisions in diagnoses of adolescents and children. It is not remotely out-of-date. It demonstrates the rapid movement of child psychopathology out of its traditional morass into its position of leadership in medicine with the precision of its conceptual methodology in clinical diagnosis.

The star-studded international collection of authors gives an overview of *DSM-III-R* and *ICD-10* (conceptual issues and empirical findings), provides a multi-chapter review of the measurement instruments (structured interviews, rating scales and checklists, observations, family assessment techniques, biological and physiological measures), and examines the validity of current definitions of certain specific diagnoses (including mood disorders, conduct disorder, attention-deficit hyperactivity disorder, and autism) in adolescents and children. Individual chapters can be read separately.

The psychometric strengths and weaknesses of all the major rating scales, checklists, and structured interviews are summarized with precision (systematic tables detail the characteristics of each instrument), giving the best available review of these commonly used measures. Particularly valuable is the discussion of standardized methods for family assessment by Jacob and Tennenbaum, since it covers techniques that are not well-known and interestingly demonstrates the "interplay of theory and instrument development." The chapter on event-related brain potentials by Courchesne and Yeung-Courchesne is a superb introduction to evoked responses and gives a careful discussion of the technique and its diagnostic potential.

The synthetic chapters are extremely strong. Cantwell's discussion of psychopathology is powerful, balanced, and scientific. The chapters on the definition and validation of mood disorders (Rutter), conduct disorder (Taylor), and autism (Rutter and Schopler) are scholarly and fascinating. The discussion by Shaffer, Gould, and Rutter on how to make a diagnostic system is excellent and contains nuggets that are useful in clinical practice. The piece by Achenbach on integrating assessment methodology into taxonomic paradigms is perhaps overly technical for some clinicians but takes on the thorny issue of comorbidity in a rigorous and useful manner.

Some sections are less useful. The discussion of direct behavioral observations is loaded with jargon and does not emphasize subtleties that a clinician might want but gives a good systematic review of techniques and raises basic issues that every clinician will want to contemplate. The discussion of biological measures is a bit superficial and uncritical, does not help the reader (unlike other chapters) understand the value or weaknesses of different biological studies, but provides an extensive review of certain biological measures in different childhood disorders. Imaging methods, drug responsiveness, and genetics research are not discussed. The section on cognitive measures does not discuss ego development, defenses, moral development, or language. Indeed, it is surprising that the whole volume goes by without discussing methods for assessing developmental stage.

Two major social issues are not covered in this comprehensive volume on diagnosis. The financial ramifications of diagnostic assessment are a big issue these days. Commercial insurance representatives and "managed care" professionals are now trying to participate in inpatient team meetings and function like team members. They would involve themselves in decisions about whether an evaluation or treatment is worth funding, state that they will fund treatment of some disorders but not others, and ready themselves to attach payments to our diagnostic labels. The biopsychosocial model is becoming replaced by a new "biopsychosocial-financial model" of evaluation and treatment.

The impact of these changes on diagnostic labeling practices merits some discussion in a modern book on diagnosis. Psychiatry has yet to come to terms with how it wants to deal with this new influence. It is worth discussing: What relationship do we want our new *DSM-IV* planning committees to have with insurance companies?

As the *DSM-IV* team plans further development of our diagnostic system, one can ask whether all our attention should still be directed on getting the details of diagnostic criteria just right. Should we not also ask how to formulate and describe the help-seeking and treatment-seeking capacities of patients and families? The course of illness for many conditions, as well as the need for intensive treatments, often depends more on the patient's capacity to use treatment and less on the patient's diagnosis. A mild but untreated depression may produce more lifetime disability than a severe depression that is promptly treated. The patient's personal ability to ask for help, to use medications as prescribed, or to show up for appointments may be more critical to the course of illness and to the treatment dollars involved than the major diagnosis. A continuing over-focus on getting precise diagnostic criteria may displace the development of an axis for help seeking or treatment seeking. Could this book have discussed the assessment of this dimension of character or ego function?

The other major social issue in psychiatric diagnosis not dealt with in this book is stigma. In a full discussion of assessment procedures, it would have been valuable to reflect on whether our assessment methods (both standardized and nonstandardized) have a stigmatizing impact on patients and families. The social and ethical implications of our developing diagnostic systems and methods may need more attention.

It is clear, though, that the editors' interests are the more traditional, central, and still developing questions in child psychopathology. This book may leave the reader with the gentle comfort of isolation—and not reminded of the social context in which medicine and health research are now advancing.

This is not a first-grader's book or a practical how-to-do-it book. It is appropriate for a seminar for advanced residents, for the end of a course in child and adolescent psychopathology, or for experienced clinicians who want a serious update on the impressive advances of recent years. Rutter says, "Classification cannot be static," and this book demonstrates with pride the remarkable achievements in upgrading psychiatric assessment of adolescents and children. Still, in the era of our new biopsychosocial-financial model, the economic and social implications of assessment and diagnosis should not be beyond discussion.

CHARLES POPPER, M.D.
Belmont, Mass.

Emotional Disturbance in Adopted Adolescents: Origins and Development, *by Ruth G. McRoy, Harold D. Grotevant, and Louis A. Zurcher, Jr. New York, Praeger, 1988, 232 pp., $39.95.*

This book is a report of a research project investigating the genesis of disturbance in adopted adolescents. The main study focuses on 50 adopted adolescents from a number of residential treatment centers and compares them with a control group of 50 matched nonadopted adolescents from the same residential centers. The investigators interviewed adoptees and their adoptive parents using a variety of questionnaires designed to investigate behaviors and dynamics of individuals and to assess a large number of factors thought to be relevant to those behaviors. These factors include parental background factors (attitudes toward parenthood and expectations of the child), child background factors (genetic risks and prenatal environment), developmental history of the child and the family (compatibility of the child and the family, communication about adoption, and traumatic family events), and extrafamilial factors (treatment and school, peer, and community support). The authors use seven theoretical perspectives to guide their organization and analysis of these factors: psychoanalytic theory, genetic theory, attachment theory, goodness-of-fit theory, cognitive development theory, adoptive kinship theory, and attribution theory.

Unfortunately, the design of the study is such that conclusions about the etiological significance of adoption in disturbed behavior cannot be made because there is no appropriate comparison group of nondisturbed adoptees. Although the study shows that issues centered on adoption (feelings of rejection by birth mother, rootlessness, and resentment about being adopted) were present in two-thirds of the adoptees, there is no evidence of their etiological significance. However, of practical importance to clinicians who must deal with these situations is the fact that such adoption issues are present and may need to be dealt with as part of therapy.

In organizing and analyzing their data according to the seven theoretical positions described, the authors manage to present and discuss a large number of factors associated with emotional disturbance in adolescents. For this overview the book is to be recommended, as well as for the attempt to connect these varied factors with the adoptive family situation. However, the study is unable to conclude which factors are particularly relevant to the adopted child's problem behavior. In their summary of study findings (pp. 160, 161), the authors conclude that "multiple poor foster placements, as well as abuse and neglect prior to the adoptees' placement, can obviate the child's development of trust in secure family relationships." Unfortunately, the discussion of the impact of multiple placements (pp. 34–36) does not contain data to support this conclusion. Because there is no proper comparison group (i.e., adoptees without psychopathology), it is impossible to show that the five children who had multiple placements had an experience that predisposed them to later behavior problems.

The practical advice given in the last chapter, "Practical Issues," is very general and not dependent on the findings of the study. The main finding that has treatment implications seems to be the failure to focus on adoption issues in the treatment situation.

REMI J. CADORET, M.D.
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Infant and Childhood Depression: Developmental Factors, *by Paul V. Trad, M.D. New York, John Wiley & Sons, 1987, 463 pp., $47.95.*

This is an interesting and important book. The title suggests a study focused on a particular age group that is also extremely broad in its conceptualization. The author straddles the biopsychosocial continuum with considerable perceptiveness and judgment.

Initially, Dr. Trad indicates the advantages of a developmental perspective for analyzing infant and childhood depression over traditional modes of diagnosing depression, noting the nature versus nurture variables within the developmental model. The biological markers for depression known up to the time of writing of this book are well described. There is an excellent description of the learned helplessness model for childhood depression, with interesting extensions into the development of self-regulation versus dysregulation and locus of control beliefs. Dr. Trad describes the process of identifying infant depression, including ways in which infants express affects, along with concepts of attachment behavior, temperamental and individual differences, and similar or dissimilar biological markers in infant depression compared with childhood or adult depression. Separation is described as a probable common pathway to depression in infancy through both attachment and separation behaviors. The nature of regulation and development of the self is then more fully introduced, with a particularly good section on neuroendocrine correlates that might affect the development of the self and a final section dealing with attachment and temperament characteristics that correlate with or predict depression.

Dr. Trad discusses defective social support and parental psychopathology as risk factors for infant and childhood depression. He summarizes the effect of parental depression on the child's self-representation, aggressive and other emotions, and cognition. There is also a perceptive section on the role of empathy in mirroring responses and on the effect of impaired parenting on empathic processes. Child abuse and neglect may cause depression, nonorganic failure to thrive, developmental delay, and defects in attachment behavior, temperament, and affective expression. Consequent effects on self-esteem may lead to violence and suicide. Three risk populations—children with depressed mothers, hospitalized children, and children who have handicaps—are compared in terms of risks. The impact of illness and hospitalization on children is summarized with particular reference to Robertson and Bowlby's sequence of protest, despair, and detachment and linked with *DSM-III* depressive symptoms. Learned helplessness is an important issue in frequently hospitalized children. Loss-of-control issues are also frequent, given children's tendencies to blame themselves for illness. Aspects of children's resilience are also described. Dr. Trad presents behavioral profiles of physically handicapped, blind, deaf, and mentally retarded children; such handicaps may enhance susceptibility to depression and depressive symptoms.

Forms of treatment for infant and childhood depression include interpersonal psychotherapy, developmental guidance and support, and infant-parent, family, and psychoanalytic psychotherapies. Each of these modalities is well described, with good references given. Particular therapies designed for hospitalized children and for seasonal affective disorder are indicated. The drug treatment of preadolescent depression is well summarized with good sections on the use of tricyclics such as imipramine and nortriptyline and with the usual reference to the paucity of studies on monoamine oxidase inhibitors.

It is difficult to make substantial criticisms of this book. There are some spelling errors in the extensive references, and the author refers to *DSM-III* rather than *DSM-III-R*. However, he was no doubt in the quandary of many publishing in 1987 about whether to update material for *DSM-III-R* purposes.

The most striking aspect of this book is its remarkably encyclopedic coverage of multiple areas of investigation in an informed and even-handed fashion. It may be that some workers with particular views would like to see more weight given to their own areas of interest, but as an overall survey of the field the book is quite excellent. It serves as a reference text about infant and childhood depression and will be widely used by those working in the field. Those wishing to start investigations in the area will no doubt want to refer to this work initially before proceeding further with their own particular interests. To this extent, Dr. Trad has performed a first-rate service in the exploration of infant and childhood depression. The book is probably too extensive for wide use among general psychiatric or child psychiatric clinicians but will certainly be useful for generalists who want to update their understanding of what is currently known in the field of infant and childhood depression. I recommend this book very highly to those with interests in the area of infant and childhood depression.

BRIAN J. MCCONVILLE, M.D.
Cincinnati, Ohio

The Psychoanalytic Study of the Child, vol. 42, *edited by Albert J. Solnit, M.D., and Peter B. Neubauer, M.D. New Haven, Conn., Yale University Press, 1987, 609 pp., $52.50.*

When I received this volume for review, I became curious about the history of this annual publication and looked over my copy of the first volume, from 1945, as well as a few of the following volumes. It is interesting to note that the managing editors have changed over the years and that only one of the original members of the editorial board, Phyllis Greenacher, M.D., remains. The high standards of this series have been maintained throughout the years. The volumes reflect the changes in ideas and the trends in research in psychoanalytic principles as they apply to children, adolescents, and their families, as well as to a number of famous people, especially authors and artists. The increasing interest in very early development of the mind during infancy and the earliest childhood is also reflected in these volumes.

Volume 42 is divided into five sections, Psychoanalytic Views of Play, Clinical Papers, Freud and Theory Building, Applied Psychoanalysis, and Psychoanalytic Education. The first section has 13 contributors who address a variety of aspects of play, ranging from the functions of play to play and reality. All are interesting and thoughtful, but one in particular caught my special attention because I had to familiarize myself with the concept of "chimeric objects and play things." The author, a third-year student at Harvard who acknowledges various sources of help, including Dr. Solnit, is to be commended for doing a good job. Several of my colleagues and I were uncertain about "chimeric objects," however. As the author explains, they are "composed of several disparate parts, each often familiar to the child but put together in an unfamiliar way." He found two of them and made one himself. The child is able to disassemble and reassemble or choose portions of them. This offers the analyst many opportunities to see how children of different ages and types of emotional difficulty handle new, unknown objects and situations.

Space limitations permit only a brief discussion of "Play and Playfulness and Survivors of the Holocaust." The authors of this chapter, who have had considerable experience in analyzing adult survivors who were children at the time of the Holocaust, present several case vignettes. The authors point out that these survivors went through a childhood experience where play was not possible. Many of them had parents before and during the Holocaust but usually clung to the "before" images. The absence of childhood play led to a variety of distortions about their own adult play as well as about the play of their children. The "requirements" they had of the analyst often meant the analyst's proving that he or she would be tolerant, patient, and understanding. For example, these patients could easily mistake normal silences on the part of the analyst for the imposed silences they had experienced as children or the stillness of their captors. Certainly the article shows, among other things, the importance of the opportunity to play in childhood.

As one reads this paper the more recently recognized and studied phenomenon of posttraumatic syndrome in Vietnam veterans as well as in children comes to mind. The individuals described here, having lived through a trauma and its sequel, could be seen as having a variety of posttraumatic stress disorder.

The section on clinical papers presents nine separate papers not related to each other but each dealing with an important topic. Of the three papers in the section entitled Freud and Theory Building, I found Peter Blos's contribution, "Freud and the Father Complex," the most penetrating. The phase Blos describes begins as the youngster tries to escape the dependency of the earliest attachment to the mother and precedes the triadic oedipal phase. It recurs in adolescence and should be worked through lest it interfere with adult adjustment. In his review of Freud's life and his own work with adolescent boys, Blos concludes that Freud did not complete this working-through process during his own adolescence but retained a strong attachment to his father that greatly influenced his life and work. Only later did he make some progress in his own maturation by better understanding and partially resolving this problem.

In view of space limitations all I can say is that the section on applied psychoanalysis contains four interesting, useful, and thoughtful papers. Not discussing them here should not indicate their lack of importance. The last section, Psychoanalytic Education, has only one paper, "Supervision of Child Psychoanalyses." It reveals the relative vagueness and lack of clear guidelines in this process. The candidate for child analysis is usually older than the candidate for adult analysis. The supervision allows for more variations according to the supervisor and his or her background. Identification, for better or worse, is often more prominent between a supervisor and the supervisee. Candidates in child analysis may run into situations that require special attention in their ongoing work or perhaps a return to analysis if they have finished this earlier. Since the child analytic candidate is farther along in his or her training, there is a need to avoid "infantilizing" him or her with too many rules or regulations and to create a more friendly, collegial atmosphere in the supervision.

I had occasion a couple of years ago to check on the number of child analysts certified by the American Psychoanalytic Association. There was an original grandfather clause in 1977 that recognized certification by the local institutes, and at that point 220 were grandfathered. About 2 years ago the number had risen to 223. Obviously, retirement and death took their toll, but newly certified candidates barely kept pace. One can only wonder if any methods will be available to make possible a more reasonable path than the current tortuous and obstacle-ridden path to psychoanalytic certification, especially certification in child analysis.

This volume, like its predecessors, is recommended to all mental health professionals who are interested in various aspects of the emotional development of children, particularly as viewed through psychoanalytic concepts; it is certainly not limited to child analysts. The contributing authors are well chosen and deal with their topics in a superior fashion.

STUART M. FINCH, M.D.
Augusta, Ga.

The Psychoanalytic Study of the Child, vol. 43, *edited by Albert J. Solnit, M.D., Peter B. Neubauer, M.D., Samuel Abrams, M.D., and A. Scott Dowling, M.D. New Haven, Conn., Yale University Press, 1988, 461 pp., $52.50.*

The Psychoanalytic Study of the Child has, since its first volume, enjoyed an unprecedented constancy of acclaim and has established itself as one of the most prestigious annuals espousing the psychoanalytic viewpoint. It has seldom been criticized.

The factors that initially made this publication prestigious are those which can be called into question, however. I am referring to the annual's parochial and stylized orientation. The early volumes were heavily weighted with papers from the New York Psychoanalytic Institute, particularly those of Hartmann, Kris, and Loewenstein. Influenced by Anna Freud and Eastern psychoanalytic institutes, the series became somewhat doctrinaire and exclusive. To maintain a scholarly orientation, many of the chapters, usually with extensive bibliographies, were pedantic, abstruse, and wordy but with little conceptually enlightening or clinically useful substance.

In recent years, this has changed, and volume 43 is a notable example of the expanded and down-to-earth orientation that *The Psychoanalytic Study of the Child* seems to have developed. As an example, this volume contains an article by Hanna Segal, a prominent Kleinian, who does not discuss Klein's theories from a scholastic, exploratory viewpoint but, instead, presents her treatment of a patient, making interpretations that would have been considered so at variance with the establishment that her chapter would have been rejected in earlier years. This volume does not have the exclusive country club qualities of earlier annuals.

There are 24 papers in this edition; these deal with theory, clinical topics, psychic development, and clinical applications. Naturally, in such a compendium, there is an unevenness of quality, but the high level that has been achieved in general is remarkable. I found the clinical section especially useful. Hans Loewald, as usual, makes an important contribution as he soberly and judiciously raises important issues concerning termination. Martin Bergmann's chapter is subtle and perceptive as he brilliantly discusses questions about the resolution of the transference neuroses. He departs from tradition in boldly asserting that the outcome of analysis does not achieve a resolution of the transference neurosis but that the analyst or, rather, the internalized analyst (what I have referred to as the analytic introject) continues to have an influence (one hopes beneficial) on the patient for the rest of his or her life. Judith Fingert Chused's chapter, although in the theoretical section, is an outstanding clinical tour de force that courageously departs from pronouncements ex cathedra about the development or lack of development of transference neuroses in children. Chused believes that if the therapist maintains an analytic perspective, children can form analyzable transferences; she effectively demonstrates this with clinical data.

I choose to mention these chapters because of my clinical bias. There are many other excellent chapters in this volume, such as the one on psychic development, which have treatment implications. Space limits discussion of other contributions that deserve commentary.

There are some chapters that are, at best, interesting but have little to contribute to the clinician. In the past, I felt it was my duty to plow through every chapter, but I sometimes felt that what I learned did not justify the effort involved in extracting meaning from what was meant to represent extensive scholarship. By contrast, this volume was a delight to read, and I can recommend it with enthusiasm. Although many of the authors are not, as yet, as well-known as those of earlier volumes, I believe this is one of the best, if not the best, of the 43 volumes of *The Psychoanalytic Study of the Child.*

PETER L. GIOVACCHINI, M.D.
Chicago, Ill.

SUICIDE

Children Who Don't Want to Live: Understanding and Treating the Suicidal Child, *by Israel Orbach. San Francisco, Jossey-Bass, 1988, 258 pp., $22.95.*

Israel Orbach, an Israeli psychologist who has studied, taught, and worked in the United States, has written a book intended to "integrate current theoretical, empirical, and clinical knowledge" of suicide in children.

Orbach sees childhood suicide as the result of a child being trapped in an insoluble conflict with his or her family. He is an emphatic believer that psychopathology in general and personality disorder in particular are not major factors in the suicide of children. He provides no real evidence for this assertion, which goes against a considerable body of work to the contrary.

Orbach's strength lies in his ability to describe family conflicts. His most extensive case description is that of the family of Sonia, a family he met after 17-year-old Sonia committed suicide. Sonia is said to have killed herself after she left home and could not live up to the high expectations she had incorporated from caring but unemotional and rigid parents. Sonia seems to have deteriorated rapidly, and there is evidence of possible psychotic depression. It is not clear why Sonia's response to her family was so different from that of her siblings. Although most people who commit suicide consider their situations insoluble, that perception is often at the heart of their psychopathology.

Orbach provides a good review of the literature dealing with what children know and feel about death. His own work supports the idea that suicidal youngsters differ from nonsuicidal youngsters in that they perceive death as less final; they think of life as continuing to function after death. Orbach sees such "defensive distortion" as needed by the child to help deal with an ongoing preoccupation with suicide.

A disproportionate amount of the book is composed of case illustrations previously published by other authors. These histories are interesting, but their impact is mitigated by the author's attempt to force them into his own conceptual framework. The case illustrations are specific and immediate, however, while the author's discussion of treatment is vague and rather abstract. A good deal of emphasis is put on increasing the death anxiety of children as a defense against self-destructiveness.

Although the book provides interesting material about the ways in which young children can be obsessed with death and suicide and provides some picture of the type of family background that contributes to their difficulties, the book does not succeed in its stated goal of integrating current knowledge. A one-sided emphasis on family conflict with little understanding of how such conflicts influence both psychodynamics and psychopathology makes the book seem too one-dimensional.

HERBERT HENDIN, M.D.
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Current Issues of Suicidology, *edited by H.J. Möller, A. Schmidtke, and R. Welz. New York, Springer-Verlag New York, 1988, 478 pp., $108.00.*

Be forewarned: this is not a very reader-friendly book. There are 63 unnumbered chapters and 112 contributors. The chapters are short, averaging less than eight pages each, including references, and there is no uniformity of format, so many chapters lack summaries and none contains an abstract. The editors provide no annotation or unification, nor do they highlight any important areas warranting further investigation.

The book suffers from all of the faults and few of the virtues of a published symposium. In the preface, the editors state that the volume resulted from the First European Symposium on Empirical Research Into Suicidal Behavior, held in Munich in 1986. Unfortunately, they fail to indicate which of the chapters come from the symposium and which were "especially prepared for this book." The faults of published symposia are well-known to most readers—chapters not tied together, inconsistent styles, general unevenness, etc. Virtues relate to the fact that publishing a symposium often gets new material to the public quickly (and it is an easy way to edit a book). It is not clear who translated this book, but I assume that the papers were given in German, and each group of authors had their work translated. All in all, the translations are good, although there are a few interesting typographical errors (e.g., "skepsis" for skepticism).

The book is appropriately divided into five sections. The first, Epidemiology and Socio-Demographic and Psychiatric Background Variables of Suicidal Behavior, consists of 16 chapters. Of particular interest here is a glimpse of some epidemiologic data from East European countries—especially the papers in this section and in some of the others pertaining to suicide rates in Hungary. Rates there have risen faster and to higher levels than they have in any other European country, and a number of investigators are studying this phenomenon. According to Ozsvath, in Budapest more women than men killed themselves in 1988.

Part two, Course and Prediction of Suicidal Behavior, presents 15 chapters. It begins with a review by Wedler of various types of follow-up studies. It includes an interesting chapter, "A Follow-Up Study: A Comparison Between Individuals Younger and Older Than 55 Years" by J. Bäuml et al., which reports that older people have a high rate of depression and concomitant recurring suicidal behavior, a low rate of attempted suicide, but a high rate of completed suicide. Younger individuals showed a high rate of positive social change, which seemed to correlate with a positive course. Changes in the elderly were more negative, such as moving to old age homes and other losses. Another study, "Changes in Hopelessness and Dissimulation in Patients After a Suicide Attempt" by Schmidtke and Schaller, attempts to investigate the lies and rationalizations that patients sometimes use following failed suicide attempts (which tend to increase with time in contrast to the apparent fact that hopelessness and ratings of intent to die decrease with time). Unfortunately, the study was inconclusive except to reaffirm that hopelessness and suicidal depressive feelings change with time after a suicide attempt.

Perhaps the most interesting section of the book as well as the most timely is part three, Biological Factors of Suicidal Behavior. Regrettably, this is also the shortest section, consisting of six chapters. It begins with an excellent review by Maria Asberg and P. Nordström. There is an interesting chapter by Arato et al., "Postmortem Neurochemical Investigation of Suicide," which, in contrast to the usual reports, found significantly higher CSF 5-hydroxyindoleacetic acid (5-HIAA) values in subjects who had committed suicide compared with control subjects. Kauert et al., in "Measurements of Biogenic Amines and Metabolites in the CSF of Suicide Victims and Non-Suicides," also did not replicate the usual finding of lower serotonin in the CSF of suicide victims. Demling et al., in "Plasma Amino Acids in Suicidal Behavior: An Investigation of Different Groups of Patients Who Attempted to Commit Suicide," found that lower plasma tryptophan may be a marker for suicidal behavior. A plasma marker, of course, would be of enormous clinical importance.

Part four, Psychosocial Factors of Suicidal Behavior, consists of 14 chapters, most of which deal with studies of life events and suicidal behavior. Schaller and Schmidtke, in "Broken Home and Suicidal Behavior: Methodological Problems," present a very thorough review of the problems in such studies. Schmidtke and Häfner, in "Imitation Effects After Fictional Television Suicides," appear to replicate some of the imitative effects described by Gould and Shaffer (1) and Phillips and Carstensen (2), except Schmidtke and Häfner found adolescent boys more prone to imitation than adolescent girls. The models used, however, were fictional males, so it would be necessary to find a fictional tragic heroine who committed suicide in order to compare subsequent rates in girls to validate this finding. "Suicide and Unemployment in Italy" by Crepet and Florenzano appears to confuse population-based and individual-based data. In showing how suicide rates in Italy correlate with unemployment rates, they cite the risk of "medicalizing" or "psychiatriazing" a large section of the population (i.e., the unemployed) rather than realizing that suicidal phenomena can be studied either microscopically or macroscopically and that the two viewpoints are not mutually incompatible. They also fail to note Brenner's work on suicide rates and unemployment (3). Kreitman presents a good review of the decreasing rates in England, Wales, and Scotland as compared with the rest of Europe in "The British Anomaly: Suicide, Domestic Gas and Unemployment in the United Kingdom." Temesvàry offers another of the interesting Hungarian studies, "Individual and Social Factors in the Psychodynamics of Suicide," in which he explores differing attitudes toward suicide in the environment of patients. This is complemented by an article by Wolk-Wasserman, "Suicidal Patients' Comprehension of Significant Others' Attitudes Towards Them."

The final section, Treatment Evaluation, has 12 chapters and largely focuses on the effectiveness of suicide centers, crisis treatments, outpatient treatments, etc. Ekeberg et al. show how the deregistration of barbiturates was followed by a significant decrease in self-poisonings by antidepressants and neuroleptics but not by benzodiazepines and other hypnotics. Szabo uses some fascinating methods in constructing "dialogograms" to depict verbal transactions, emotions, and facial expressions during videotaped interviews. Aside from the scientific merits of the study, I took extreme exception to his comment that "with the aim of studying the very nature of patients' communicative behavior, we avoid bargaining about consent [to videotape] before the conversation. From an ethical viewpoint, we think that it is not the fact of recording information that is most important but the handling of the material recorded." I hardly think that the ends justify the means of videotaping without permission. The development of a suicide attitude questionnaire is presented by Diekstra and Kerkhof in the book's final chapter. Such a scale may prove to have very useful predictive value regarding suicide.

I cannot recommend this book to the general reader. The serious student of suicide may find it worthwhile, particularly because it provides a glimpse into what is going on in Europe, especially those countries which have seemed more concealed from the student of suicide. A little more sensitivity to the reader's needs and a little careful editing and annotating would have gone a long way toward making this a much more useful volume.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Possible Toxicity of Combined Fluoxetine and Lithium

SIR: Potentiation of antidepressants with lithium carbonate has become a common tactic in our clinical armamentarium (1, 2). Recently, Pope et al. (3) reported on the possible synergism between fluoxetine and lithium in refractory depression. We would like to report the following case of possible toxicity from the combination of fluoxetine and lithium carbonate.

> Ms. A was a 53-year-old woman with a diagnosis of major depressive disorder who was only partially responsive to tricyclics and fluoxetine. At the time she was admitted to our hospital with a 2-year history of depression, she was taking fluoxetine, 20 mg each morning, and lorazepam, 0.5 mg q.i.d. She had been taking the fluoxetine for 2 months, with marginal relief. Lithium carbonate, 900 mg/day, was added to her regimen in hopes of augmenting the action of the fluoxetine. Within 48 hours, the patient became increasingly confused. She developed ataxia, falling but never losing consciousness. She was unable to respond to simple commands. Her right arm demonstrated a coarse tremor. She was poorly coordinated and did not seem purposeful in her movements. She held her legs in a flexed position and extended them in random fashion, with occasional pelvic thrusts as well. She could not sit, walk, or stand unaided. Her breathing became ratchety. Her rectal temperature was 101 °F. Results of laboratory tests were normal except for a leukocyte count of 17,300/mm^3 and a minimally elevated bilirubin level of 1.4 mg/dl (normal=0.2–1.2 mg/dl). An EEG was done shortly after the onset of symptoms and another was done 4 days later; both were normal. A CT scan of the cranium was normal.
>
> The lithium and fluoxetine were stopped within several hours after the onset of Ms. A's symptoms. (Her lithium levels had ranged from 0.80 to 1.12 meq/liter.) Her symptoms improved briefly but then reemerged, prompting her transfer to the neurology intensive care unit. The patient's condition became normal over the next 4 days. Along with this improvement she had total remission of her depressive symptoms, reporting that she felt better than she had in 2 years. She was subsequently discharged but returned depressed 1 month later. She ultimately responded to lithium carbonate (levels=0.65–1.08 meq/liter) and nortriptyline in combination without any significant deleterious effects.

During clinical trials with fluoxetine, 34 patients also received lithium without any adverse drug reactions noted (personal communication from the Eli Lilly Research Laboratory). Pope et al. (3) noted no adverse interactions in five patients taking a combination of lithium and fluoxetine. A case of elevated lithium levels with subsequent severe toxicity induced by combined fluoxetine and lithium was recently reported by Salama and Shafey (4). In our patient the lithium never reached toxic levels. The patient later took lithium carbonate again at comparable levels without untoward effects. We think it is possible that this patient's symptoms represented a toxic encephalopathy induced by the combination of fluoxetine and lithium carbonate.

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Mania Induced by Fluoxetine

SIR: While fluoxetine, a recently approved serotonin reuptake inhibitor, is known to produce anxiety and insomnia (1), its ability to induce mania (1–3) appears less well-known than that of its noradrenergic predecessors. Although this underappreciated propensity is perhaps due in part to the fact that fluoxetine was only recently approved and so far has not been widely used, it may also be related to the widespread belief that the mania-inducing effects of antidepressants arise principally from noradrenergic mechanisms (4). We recently treated a patient whose response to fluoxetine reminds us that fluoxetine can, like its noradrenergic predecessors, induce mania.

> Ms. A, a 71-year-old grandmother, was brought to the geriatric psychiatry clinic of our hospital after she suddenly and uncharacteristically began to spend money excessively, neglect her self-care, and act as if she were "high." Ms. A had been treated for a recurrent, unipolar major depressive disorder 17 years earlier and again about 7 years ago, at which time she had been hospitalized and treated with amitriptyline. After discharge she had been treated with alprazolam and counseling. At no time during her long history of depression had she experienced mania. During her most recent depressive episode, she had been treated with fluoxetine (20 mg/day) added to a stable regimen of temazepam (30 mg h.s.), alprazolam (0.5 mg t.i.d.), and Dyazide (one capsule every day). She had no

history of drug or alcohol use, nor had she experienced acute stress that would have been likely to induce her manic symptoms.

Within 10 days of the beginning of treatment with fluoxetine, Ms. A's depressive symptoms began to improve. Forty days later, however, she began to exhibit a manic syndrome characterized by pressured, tangential speech, impaired attention with distractibility, grandiosity, elation, impulsivity, sleeplessness, and irritability. The fluoxetine was stopped. A week later her daughter called to report that the patient was spending money excessively, writing checks without regard to her bank balance, and attempting to tear out walls and dig up the bushes in her yard. She was hospitalized and started on a regimen of haloperidol (1 mg t.i.d.) and lithium carbonate (300 mg b.i.d.). After 7 days the manic symptoms started to subside, and by the 14th day she was free of these symptoms. She was not given a rechallenge test with fluoxetine.

The nature and timing of our patient's response to fluoxetine are consistent with drug-induced mania and accord with previous reports of fluoxetine's mania-inducing effects (1–3). Although the mechanism is obscure, it is possible that these effects arise from enhanced serotonergic neurotransmission, since fluoxetine is devoid of noradrenergic and dopaminergic effects (5). Regardless of the mechanism, clinicians should be aware that the selective serotonergic effects of fluoxetine, and perhaps other serotonergic antidepressants, do not preclude mania-inducing activity.

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Plan for Private Insurance Coverage of Mental Disorders

SIR: We would like to report what we think is a first and a model in private insurance coverage of mental disorders. The University of Texas Chairmen of Departments of Psychiatry designed the plan in collaboration with the University of Texas System's office and the American General Insurance Company. It allows the doctor to treat a patient in or out of the hospital as the patient's illness requires and allows the patient to follow the prescribed course of treatment without having to pay more as a consequence of outpatient treatment. By providing flexible benefits that do not tie payment of the doctor's fees to hospitalization, it separates the doctor's interests from those of the hospital; indeed, it may even provide a small financial incentive for outpatient treatment.

The previous University of Texas plan called for hospitalization coverage of up to 30 days per year and a $1,500 maximum of outpatient coverage. It also provided for 30 days of nonresidential care and allowed a one-for-two exchange of hospital days for day-treatment days. Patient cost sharing and provider reimbursement were the same as for other illnesses except that coinsurance payments did not apply to maximum out-of-pocket limits (the point at which coverage for catastrophic illness goes into effect). The plan also carried programs for the treatment of drug and alcohol abuse, but these are not the subject of this communication.

The new program expands psychiatric coverage of outpatient visits for medical management of serious mental disorders as follows. 1) A medical management visit is defined as a brief, 20- to 25-minute visit for a diagnosed mental illness, as defined in the latest edition of *DSM*, in which the physician evaluates the patient's condition with regard to whether medication should be initiated, discontinued, adjusted, or monitored; such definition, of course, does not preclude other supportive intervention that may be indicated. 2) Up to 15 hospital days may be exchanged on the basis of three brief medical management outpatient visits per hospital day per year, up to a maximum of 45 visits annually. The per-visit charge cannot exceed 65% of the established and acceptable charge for a 45- to 50-minute visit. All exchanges must have prior utilization management approval, and a diagnosis must be submitted as a condition of reimbursement. Nonresidential or day-treatment coverage is not exchangeable for medical management visits. 3) The $1,500 benefit of the previous plan remains as an additional benefit to cover, without prior approval, outpatient psychotherapy and such other needs as more extensive medical evaluation, extended family evaluation, and the like.

The program still has limitations: coverage, especially for psychotherapy, is not as unlimited as for other areas of medicine; care is managed; and coinsurance payments do not apply toward the patient's maximum out-of-pocket expenditures. Also, at present the program is only available to the roughly 100,000 persons who are employed by or are dependents of those employed by the University of Texas system. Nonetheless, the new program is a considerable advance. For example, it would allow a patient to be hospitalized for 12 days, then to be seen twice a week in the doctor's office for 3 weeks, then once a week for 3 weeks, then once a month for 4 months, and still have 10 remaining days of covered hospitalization in the same year if his condition should require it. If longer visits, more visits, or more extended outpatient evaluation becomes necessary at any time, the $1,500 psychotherapy benefit may be drawn upon. The patient could also utilize a nonresidential day center, as necessary, up to 30 days.

Unless an illness starts in January and is unusually severe (in which case any limited plan is inadequate), the new plan should cover adequate and appropriate care in a given year of onset and in subsequent years. With proper control through utilization management, it may well turn out to be less expensive than the earlier plan, which is typical of those currently available. We will be working closely with the company to monitor the plan and determine whether this is so. If successful, the program may be modifiable later so as to allow coinsurance payments to count toward a patient's maximum out-of-pocket expense and thereby provide a still better safety net as well as better coverage for those suffering from psychiatric disorders.

We hope *Journal* readers will find this of interest.

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Quality of the Psychiatric Literature

SIR: We are writing to bring up a topic of continuing importance to scientific progress in psychiatry: the quality of our literature. Specifically, we are very concerned that although the literature is becoming more "quantitative," statistics are being used to dress up marginal work or pilot studies. To illustrate, we analyzed a recent issue of the *Journal*, of *Archives of General Psychiatry*, and of *Hospital and Community Psychiatry* (*H&CP*).

Of the 24 experimental studies reported in these issues (11 in *Archives*, 11 in the *Journal*, and two in *H&CP*), 38% had experimental groups smaller than the usually accepted norm of 20 cases. Sixty-three percent analyzed subgroups of less than 20 cases. Studies from the National Institute of Mental Health were by far the worst offenders. Twenty-one percent of studies that should have had a control group had none. When "matched" control subjects were used, only 30% of the studies reported how the matching was done.

In only two of the 24 studies was there a probability selection of cases (one each in the *Journal* and in *H&CP*), and in only two studies was there a correction for multiple statistical tests (both in the *Journal*). Seven studies had more variables than cases, a violation of a basic statistical tenet.

It is often correctly argued that there is no perfect study. But some authors apparently believe that to produce a valid research report, they need only discuss the limitations of the methods and statistics they use, rather than deal with the limitations. Even accepting this logic, only 13 of 24 authors mentioned methodologic limitations, and only five mentioned statistical limitations (usually a small sample size).

There also seems to be an ethic in the literature that all that is necessary to produce a quality research report is to use a few statistical tests. There appears to be little concern about small sample sizes, control groups, matching, or the proper use of statistics. Often, the result is a brief case report that is presented as something more profound by adding a few t tests.

Our points are that, first, we are fooling ourselves about the rigor of many of our research reports, buying into our own quantitative "snow job." Psychiatric researchers (and journal reviewers) need to recognize this simple fact and be more rigorous.

Second, there is nothing wrong with case reports, descriptive reports, and preliminary reports of a few cases. What researchers need, however, is permission (from themselves and journal editors) to present these reports for what they are, rather than presenting each study as though it were a valid quantitative report on a subject. This would place the work in proper perspective, allowing the field to properly evaluate the relative importance of the study. This would also encourage more clinically oriented colleagues to disseminate their observations through case reports, so these observations could be subsequently studied more rigorously.

We recognize that in recent years the *Journal* has done much to upgrade its statistical review of manuscripts. We would suggest, however, that it and all psychiatric journals need to further upgrade the methodologic review of manuscripts and to present both good quantitative and good nonquantitative work as such, rather than trying to fit all studies into the "statistically valid" mold.

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Ed. comment: In recognition of the importance of quality in research, in September 1987 the *Journal* initiated a program of statistical review of all manuscripts not rejected outright for other reasons (see *Editorial*, August 1988, pp. 987–988).

Mnemonic Device for Criteria for Borderline Personality Disorder

SIR: We have seen borderline personality disorder present itself in many different ways in clinical settings. Like many other clinicians, we have discovered that early diagnosis of this axis II disorder is very helpful in preventing and managing transference/countertransference complications. As it is difficult to keep in mind all eight of the *DSM-III-R* criteria for borderline personality disorder, we have developed a mnemonic device to aid our recall of these criteria.

One characteristic of patients with borderline personality disorder is their ability to drain the emotional resources of their therapists. Our mnemonic brings this concept to light by using the word "sap." The mnemonic is *I'm a sap, i.e.*, borderline: *I*mpulsiveness, *m*oodiness (affective instability), *a*nger, *s*uicidal threats, *a*bandonment, *p*attern of unstable relationships, *i*dentity disturbance, *e*mptiness. In the midst of a clinical interview, easy recall of these criteria can lead to more focused inquiry and increased diagnostic accuracy. Our staff has found this device to be quite useful.

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Diagnosis and Treatment of Depression

SIR: Questions raised by Mogens Schou, M.D., concerning diagnosis and treatment of major depression in the United States (1) can be addressed by multinational research monitoring speech pause time, a behavioral correlate of mood (2). This method transcends language differences, since the temporal structure of adult dialogue and its affective correlate are prelinguistic (3). Pauses processed on a time base are precise, objective measurements to aid in answering Dr. Schou's questions about whether American psychiatrists are unable to distinguish between neurotic or chronic depression and recurrent depressions with symptom-free intervals, whether they are too impatient to wait for the sometimes gradual onset of the prophylactic action of lithium, and whether unipolar illness is diagnosed differently on the two sides of the Atlantic.

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Intrusion and Avoidance Symptoms in PTSD

SIR: The relationship between the intrusion and avoidance phases of posttraumatic stress disorder (PTSD) has been the subject of much speculation over the years. Usually, such speculation has focused on the important role intrusion symptoms play in initiating and/or maintaining avoidance symptoms (1), so it was with interest that I read the findings of Julia B. Frank, M.D., and associates (2). Using the Impact of Event Scale, they found that intrusion symptoms substantially improved or decreased, whereas avoidance symptoms did not, during medication trials with phenelzine or imipramine in their sample of war veterans.

This is not the first such observation. A medication study of civilian patients with acute PTSD also reported the same differential efficacy (3). Cella et al. (4) used the Impact of Event Scale to measure the stress responses of a group of burn victims' relatives who were not in treatment. These investigators reported that the intrusion item scores decreased, over time, more dramatically than the avoidance item scores. Horowitz et al. (5), also using the Impact of Event Scale and working with a mixed trauma group, found a correlation of 0.42 ($N=66$, $p>0.0002$) between intrusion and avoidance items. Zilberg et al. (6), however, working with an acute bereavement group, found a correlation of only 0.15 ($N=30$, $p<0.40$), far less than a perfect linear relationship. To date, then, many of the available empirical studies have failed to document a relationship between the intrusion and avoidance phases of PTSD.

I undertook a study of two groups of PTSD patients (diagnosed according to *DSM-III* criteria) who were experiencing acute symptoms secondary to either a sudden loss or a motor vehicle accident to determine whether and to what extent a relationship could be documented. The study groups consisted of 37 PTSD/loss patients (12 male and 25 female) and 42 PTSD/accident patients (nine male and 33 female). Their average ages were 41.7 and 39.0 years, respectively. They were seen in a private-practice office setting as necessary. All were given the Impact of Event Scale, and the elapsed time from trauma until initial interview was noted. The Impact of Event Scale results were submitted for statistical analysis to determine the correlation coefficients for the intrusion and avoidance subtotal scores.

The average Impact of Event Scale scores for the PTSD/loss group were intrusion, 27.57; avoidance, 21.05 (average trauma-to-interview interval, 24.35 weeks); $r=-0.19$, $df=35$, $p<0.25$. The average Impact of Event Scale scores for the PTSD/accident group were intrusion, 27.60; avoidance, 23.74 (average trauma-to-interview interval, 22.79 weeks); $r=0.20$, $df=40$, $p<0.20$. In neither group was the correlation coefficient significantly different from zero. The groups did not significantly differ on the demographic or trauma-to-interview interval variables. These findings, as well as the reports mentioned earlier, suggest that meaningful factors other than intrusion symptoms contribute to the maintenance and perhaps the initiation of PTSD avoidance behaviors.

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Patient-Therapist Sex

SIR: The assertion by Thomas G. Gutheil, M.D., that he was studying "the patient-therapist dyad in clinical terms" rather than "blaming the victim" (1) is not entirely convincing. He portrayed the patient who is most likely to be the victim of a therapist's sexual misconduct or other sorts of boundary violations as one whose rage is so intimidating that "even experienced clinicians" dare not deny her demands, whose confusion about boundaries "may induce similar confusion in therapists," and whose "powerful interpersonal manipulative skills" may induce therapists to do "what they should know better than to do." He stated that "patients with borderline personality disorder possess the ability . . . to seduce, provoke, or invite therapists into boundary violations . . . in the countertransference" and followed this assertion with a number of clinical vignettes apparently intended to illustrate this point. In fact, these examples revealed nothing more than that the therapists (such as the therapist who asked his patient to edit his professional articles) were themselves gravely confused about the boundaries of the therapeutic relationship.

In a recent article on violence against women (2) Lenore Walker reminded us that, historically, rape victims have been blamed for engaging in behavior which caused their rapists to lose control, and sexually abused children have been seen as provocative or seductive. Apparently unable or unwilling to believe the extent of the sexual abuse his female patients had suffered, Freud shifted the focus onto the oedipal longings of these patients and away from their abusers. As the magnitude of the problem of sexual exploitation of patients by therapists begins to become apparent, it is predictable that the profession will seek to deflect the impact of these revelations by subtly shifting the burden of responsibility at least partially onto these patients. Could Dr. Gutheil's borderline patient be the latest incarnation of the myth of the seductive child?

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Dr. Gutheil Replies

SIR: I believe it was Kinsey who said that the mark of a mature intellect is that it can entertain two contradictory ideas and still continue to function. I hoped for such intellects in my readers and sprinkled my article with caveats for the rest. However, it appears that I must push clarification to its pellucid limit.

First, the doctors in my article (in the true cases, of course) were wrong, *and* the patients evinced the behaviors that were discussed. The doctors committed ethical, clinical, and legal violations, *and* the patients played a role in them. The doctors committed malpractice, breached the fiduciary relationship, abused a power asymmetry, and exerted undue influence, *and* the patients initiated some of those actions. Only from a very limited perspective would it seem that to study the patient's role and responsibility must somehow subtract from the doctor's unequivocal culpability, as though some moral zero-sum game were involved.

Second, those who work in training settings and do extensive consulting work might educate Dr. Beal about how common it is for trainees and young practitioners to struggle with borderline patients over boundaries, to be sorely tempted, to skirt—barely—the abyss. Only by understanding patients' behavior can responsible clinicians learn how to stay out of trouble (the "pitfalls" in my title). My article was aimed at such greater understanding.

Finally, Dr. Beal's position offends me as a feminist. Does she see these women patients as ciphers, as puppets, as incompetents, as children indeed, as her last sentence (perhaps unconsciously) reveals? I cannot concur. *Although the doctors were culpable and the patients were not*, both were voluntarily in bed. To pretend otherwise is to demean further these already victimized women.

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The Psychiatric Trainee as an Executive in Training

SIR: Michael A. Silver, M.D., and Luis R. Marcos, M.D., dealt with a significant yet commonly overlooked topic in their article entitled "The Making of the Psychiatrist-Executive" (1). As I reviewed the article with trainees, it became apparent that this issue did not have the same immediacy as issues of patient care or research. Management? They didn't become psychiatrists to become managers or executives.

As any psychiatrist who has a practice or works for a university or a private or public hospital knows, the business of medicine is inseparable from the practice of medicine. To relinquish the control of business decisions is to leave our patients at the mercy of the forces of the marketplace. Few trainees, given their developmental needs, become aware of the importance and the impact of administrative skills on the implementation of care until after they have left their training institution and joined the work force. However, it is unlikely that either training programs or trainees will incorporate administrative training into their curriculums or, more importantly, into the delivery of everyday care unless it has immediate consequences.

The time for training in administrative skills is in the residency years, and the place is in the management of patient care. Further, it should be seen as training to be received by all psychiatrists, not just the psychiatrist-executive. All clinical work in which others are involved requires the utilization of administrative skills. The question "Who is an executive?" was answered by Peter Drucker: "Anyone who . . . by virtue of his position or knowledge . . . is responsible for a contribution that materially affects the capacity of the organization to perform and to obtain results" (2). All psychiatrists, regardless of rank, level of training, or site of care, are executives in the determination, delivery, and quality of care received by their patients.

I propose that all training programs, regardless of orientation, incorporate administrative, management, and executive training into every level of training. The principal aspects of the training should be 1) time management, 2) focus on results rather than the work to be performed, 3) setting priorities, 4) effective decision making, 5) managing change, 6) communication skills, and 7) determining competitive market strategies (3, 4). In the article by Drs. Silver and Marcos, a number of these items were described as personality traits. I disagree. Characteristics such as the ability to create a focus, concentration on outcome, good communication skills, and the ability to synthesize from the theoretical to the practical, to list just a few, are as learnable as the recognition of transference, countertransference, and resistance.

As psychiatry becomes more stratified and subspecialized, there needs to be a concentrated effort to provide a focus that encompasses the scope of its diversity and potential. The emphasis on management would provide a higher order of organization, bringing together clinical and research areas under a common mantle. Executive training should be seen for its true value, which is as an indispensable aid in the management of the development of the field of psychiatry.

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NORMAN E. ALESSI, M.D.
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Drs. Silver and Marcos Reply

SIR: We concur with most of the ideas espoused by Dr. Alessi in his letter. In fact, his observations of his trainees reinforce the results of a recent study which found that young psychiatrists are not choosing to become administrators either immediately after residency or 5 years into their careers (1). At the other end of the career ladder, in a recent study of 244 psychiatrist-executives, we found a large discrepancy between their actual career experiences and what is perceived as ideal preparation in the areas of formal administrative training and mentoring relationships for a career as a psychiatrist-executive (2).

Together with Dr. Alessi, we strongly support the notion of incorporating administrative training into the residency curriculum, especially in the areas of formal administrative training and mentoring relationships. We have four suggestions with respect to how this can be implemented.

First, psychiatric residents should be offered a separate administrative track in the residency and comprehensive administrative fellowships (3). The structural components would provide intensive training in management theory and business techniques and supervised administrative experiences with psychiatrist-executives who, as mentors, could influence the development and career paths of aspiring psychiatrist-executives.

Second, training programs should consider assigning, through a matching process, a senior psychiatrist as a mentor to each resident. The matching process could pair psychiatrist-executives with residents interested in administration.

Third, resident training programs could integrate a compulsory administrative rotation into their core curriculums. This would have the benefit of exposing all residents to administration, so that the choice of an administrative career could be based on education and experience.

Finally, a relationship between a master's program in business administration or public administration and a psychiatric resident training program could be developed. This type of program would allow prospective psychiatrist-executives to develop their management skills through both didactic training and increasing administrative experience in the clinical setting. At the completion of the program, the individual would have an advanced administrative degree and be prepared for commencing a career as a psychiatrist in an executive position.

We believe that as a consequence of any or all of these programs, psychiatrists would be better prepared for the executive role which most psychiatrists encounter at some time in their careers. Of equal importance, resident psychiatrists could consider careers in administration and address management issues in the mental health care industry in a more pragmatic and realistic fashion.

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MICHAEL A. SILVER, M.D.
LUIS R. MARCOS, M.D.
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The Treating Psychiatrist as Expert Witness

Sir: Brian F. Hoffman, M.D., and Harvey Spiegel, LL.B. (1) offered a concise and valuable guide to the legal principles involved in litigants' efforts to recover psychological damages and to the psychiatrist's role in evaluating and testifying in cases brought by plaintiffs who claim such injuries. I would appreciate these authors' response to the following comments about problems that arise when attorneys ask *treating* psychiatrists to provide expert testimony, especially when treatment has been initiated without any prior understanding that such testimony might be requested.

The section on impartiality and objectivity in the American Academy of Psychiatry and the Law's "Ethical Guidelines" (2, p. 17; cited by Dr. Hoffman and Mr. Spiegel in their reference 17) states, "A treating psychiatrist should generally avoid agreeing to be an expert witness or to perform an evaluation of his patient for legal purposes because a forensic evaluation usually requires that other people be interviewed and testimony may adversely affect the therapeutic relationship." Robert Simon (personal communication, 1987) has recommended that treating clinicians consider making written agreements with patients involved in litigation so that the clinician's role will not be blurred.

Beyond the potential feelings of betrayal or other practical effects on the treatment relationship that might follow forensic evaluation or testimony lies an additional problem: successful psychiatric treatment often rests on philosophical principles that may be antithetical to the procedures and claims involved in personal injury litigation. Patients expect their treating physicians to see things from their point of view and to be advocates for their individual interests. To make useful assessments and to have courtroom credibility, however, forensic clinicians must evaluate plaintiffs from an objective stance. Forensic clinicians may be advocates, but they generally argue for the soundness of their conclusions, not for one of the parties to a legal dispute.

Especially in psychotherapeutic treatment, clinicians often hope to enhance patients' well-being by helping them master their own difficulties and by increasing patients' autonomy through mutual discovery of conflicts, deficits, cognitions, behaviors, and desires that impede optimal functioning. Improvement thus depends in part on patients' accepting responsibility for their predicaments and for getting themselves out of them. The essence of tort litigation is to place that responsibility elsewhere. This is not to say that patient-litigants seek only "green poultice" remedies for their suffering or that the issues of legal and psychotherapeutic responsibility cannot be teased apart, but having one psychiatrist serve as both treater and evaluator may make resolving such issues more difficult.

I have found it hard to convince attorneys that my treatment-based evaluations of their clients would not meet forensic needs and that my serving as an expert might subvert ethical principles as well as therapeutic and legal goals. Perhaps attorneys' expectations are based on their experience with physicians in other specialties, for whom treatment of and testimony about physical injuries do not involve the potential conflict of interest generated by psychological damage litigation. Attorneys also may not wish to pay for or subject their clients to a separate forensic examination, even though undergoing such an examination should be in their clients' financial and emotional interests.

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DOUGLAS MOSSMAN, M.D.
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Dr. Hoffman and Mr. Spiegel Reply

SIR: Dr. Mossman summarizes the dilemmas that arise when a treating psychiatrist is asked to provide expert testimony about his or her patient. In fact, this covers two very different situations—a request to provide information or a request to do a complete assessment for litigation purposes. In the first situation, all physicians, including psychiatrists, are obliged to provide the requested information to the lawyer within a reasonable period of time. The lawyer needs this information to pursue a litigation claim, and a just and timely settlement would be impossible without it. In Ontario, failure to provide a report to a lawyer within a reasonable time is considered to be unprofessional conduct on the part of the physician.

In the second situation, a treating psychiatrist is under no obligation to do a complete forensic and litigation assessment of a patient. An example of a partial response to a lawyer requesting such information could read: "The patient was in therapy for depression or chronic pain and was seen on the following dates . . . . The patient received the following treatment . . . . Because of the nature of the therapeutic relationship, it is difficult for me to make statements about the etiology of the patient's condition or about prognosis, and I would recommend strongly that the lawyer seek an independent assessment from another psychiatric consultant."

Similarly, when a consultant becomes aware of the need for therapy during a legal assessment, the consultant should generally refer the patient to another therapist but offer to see the patient again at the request of the patient's lawyer if a progress report is required later.

Psychiatrists occasionally see patients who enter therapy and "forget" to mention their involvement in litigation proceedings. Consciously or unconsciously, these patients are looking for an advocate. The patient can be told that the psychiatrist will respond only to a lawyer's written request for information and that any report will be confined to relatively factual information. Questions about cause and prognosis may have to be directed to an independent consultant.

Nevertheless, no treating psychiatrist can escape the possibility of a subpoena from a plaintiff's or defendant's counsel to produce clinical notes or testify in court. This may raise questions of confidentiality and therapeutic privilege for psychiatrists that are handled differently in various jurisdictions.

Although most psychiatrists would prefer to separate the roles of therapist and objective, unbiased consultant, the lawyer coauthor of this reply is tempted to question the wisdom of the ethical guidelines referred to by Dr. Mossman and would argue that the roles of therapist and expert witness are not always irreconcilable. Instead of applying a blanket rule, he feels that the options must be weighed in each case. In some cases the therapist may be the best person to write a favorable expert opinion for the patient, and this would not harm the therapy. If the report might be unfavorable, then the patient should be involved in the decision, as it is in his or her interest to get a fair and timely settlement of the claim.

Not surprisingly, the professions hold different opinions on these thorny topics.

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HARVEY SPIEGEL, LL.B.
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Empirical Study of Empathy

SIR: Leslie Brothers, M.D. (1) has undertaken the formidable task of integrating the complex psychological components of interpersonal phenomena with neuroscience principles. We concur that a major difficulty in neurobehavioral research is the clear definition of complex human phenomena such as empathy. However, we wish to emphasize the importance of precise definitions, as they lend themselves to broader, more refined experimental analysis of human brain-behavior relationships. Such specificity facilitates valid and reliable measurement of behavior, comparison to related psychological processes (e.g., sympathy, identification, language), and correlation with neurodiagnostic data in the quest for the neurobiological bases of human behavior.

Dr. Brothers used the term empathy "in discussion of interpersonal phenomena" (p. 11). Her review of more precise definitions of empathy reflects predominantly psychoanalytic perspectives, which unfortunately have not led to the development of standardized methods for assessment. The results of numerous psychological investigations, building upon more than 50 years of construct identification, elaboration, and measurement, have led to such development and were omitted from her review. These accumulated data suggest that empathy is a multidimensional construct which has been observed and measured with reasonably good reliability and validity. Essentially, empathy involves a sensitivity to the emotional experiences of others which contributes to the potential for sharing and increased understanding through an interpersonal relationship. Two distinct components of empathy have been proposed: affectively based empathy and cognitively based empathy. These can be differentiated psychometrically, are amenable to measurement, and hence permit use in empirically based research (2, 3).

Affectively based empathy refers to the ability to construct for oneself another's emotional experience. It involves vicarious arousal and experience of another's feeling state. Available data suggest that affective empathy may reflect a basic process present in infants and young children and seems to predate development of—and later accompany—the cognitive components of empathic understanding.

Cognitively based empathy involves the ability to take another's viewpoint, infer that person's feelings, or put oneself in his or her shoes. Essentially, it involves the ability to construct for oneself another person's mental state. From this standpoint, such processes as perspective-taking ability and spatial reasoning have been proposed as potentially important factors in empathic ability.

Utilizing some of the available measures of empathy has allowed us to study the construct directly, rather than by inference, in patients with focal brain lesions. Preliminary studies in our laboratory of cognitively based empathy have suggested that many brain-injured patients are capable of reliable self-report with some of the empathy measures, and that alterations in other mental processes such as cognitive flexibility (4) and perceptual judgment may provide some of the important cognitive underpinnings for reduced empathy levels. In our evolving model, the neurologic substrate of empathy encompasses multiple brain areas, operating as a system and involving posterior sensory, motor, limbic, and prefrontal lobe structures.

We believe that the available psychological and psychiatric literature, coupled with modern neurobehavioral research methods, can increase our understanding of empathy, with possible implications for diagnosis and treatment interventions in psychiatry, neuropsychiatry, and psychology.

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LYNN M. GRATTAN, PH.D.
PAUL J. ESLINGER, PH.D.
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Dr. Brothers Replies

SIR: Drs. Grattan and Eslinger rightly point out that reliable and valid clinical measures of empathy are essential for studying empathy as a dependent variable in patients with brain lesions. While my paper addressed mainly the mechanisms of affective empathy, the cognitive aspect to which Drs. Grattan and Eslinger refer is also of great interest. Regarding its evolution, we clearly have much to learn from the observations of primatologists such as Smuts and De Waal, as I hope to show in forthcoming work.

The published abstract of Drs. Grattan and Eslinger's empirical findings in patients with brain lesions (reference 4 in their letter) stimulates anticipation of their further development of this important line of neuropsychological investigation.

LESLIE BROTHERS, M.D.
Los Angeles, Calif.

Genetics and Idiopathic Schizophrenia

SIR: Herbert Pardes, M.D., and associates, in their comprehensive overview of genetics and psychiatry (1), noted that the original method for identification of abnormal genes—through first finding their abnormal protein products—"has not yet fulfilled its potential" in neuropsychiatry "because in all but a few instances, the metabolic concomitants . . . are still unknown." The authors did not mention the possibility that identification of the environmental factors *necessary* for phenotypic expression of idiopathic schizophrenia might provide clues to the abnormal gene products and their metabolic concomitants. I have recently summarized this approach to the genetics of schizophrenia and ways of testing it (2).

Much evidence indicates that the environmental factors necessary for expression of the phenotypes of idiopathic schizophrenia are the opioid peptides (exorphins) produced by enzymatic action on glutens in cereal grains. These potent opioid peptides were sought—and found—in glutens by National Institute of Mental Health basic scientists (3) because of evidence that gluten was a causal factor in schizophrenia.

Other major findings (2) suggesting that glutens play a necessary role in evoking idiopathic schizophrenia are 1) the extreme rarity of overt schizophrenia in populations that do not consume cereal grains, 2) the high correlation between rates of wheat and rye consumption and rates of first admissions to mental hospitals of women ($r=0.98$, $p<0.001$) and men ($r=0.86$, $p<0.02$) with schizophrenia, 3) randomized clinical trials indicating that absence of glutens hastens improvement of acute and relapsed schizophrenic patients, but only an occasional long-term, neuroleptic-resistant schizophrenic patient responds, 4) the increased urinary excretion of small peptides, some with opioid activity, by schizophrenic persons, 5) many observations suggesting that schizophrenia and celiac disease, a disorder irregularly evoked by glutens, share some but not all genes, 6) the finding that a specific gluten peptide fraction produced stereotyped behaviors and limbic seizures in rats hours after intracranial injection, and 7) recently, the finding that chronic high gluten intake produced neurochemical changes in cats' brains similar to post-mortem findings in schizophrenic patients (4).

On the basis of the evidence, I hypothesized (2) that abnormal alleles at a few complementary polymorphic loci produce aberrant enzymes and receptors. Their combined effects markedly increase the probability that gluten exorphins (or their precursors) will pass in a gluten-dose-dependent fashion from gut to brain. There, schizophrenia-specific abnormal opioid receptors with increased affinity for gluten exorphins would permit low ambient concentrations of exorphins to cause dopaminergic and cholinergic dysfunction that evokes the spectrum of schizophrenic phenotypes.

My hypotheses are testable at many levels. For example, aberrant enzymes likely to cause decreased catabolism—possible endophenotypes—of the highly hydrophobic exorphins (i.e., neutral endopeptidase, the structure of which is known, pyroglutamyl peptidase, and angiotensin-converting enzyme) deserve careful measurement. Decreased activity of the last two in schizophrenic patients has already been reported (2, 5).

Thus, for the majority of schizophrenic persons, the easiest route to identifying genes that produce susceptibility to schizophrenia may be through study of abnormal receptors and enzymes which increase the likelihood that exorphins will distort brain function. However, the most practical advantage of testing my hypotheses is that if they are on target, the prevention and treatment of early schizophrenia would be considerably improved.

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F. CURTIS DOHAN, M.D.
Philadelphia, Pa.

Dr. Pardes and Associates Reply

SIR: Dr. Dohan makes a useful contribution by proposing a specifically testable hypothesis for the epigenesis of schizophrenia. Its heuristic value lies both in the fact that it is operational and in its recognition of the likely interplay between biological vulnerability and environmental stressors (1).

However, we must be temperate in our evaluation of existing data. The evidence Dr. Dohan provides is indirect, and there are alternative explanations for the phenomena he describes. For example, he suggests that the epidemiological observation that schizophrenia is rare among certain Pacific island populations, where no grain or cow's milk is consumed, supports an etiologic role for exorphins in schizophrenia. An alternative, equally plausible explanation might be that individuals on these islands are geographical isolates, some of whom have been spared a genetic risk for schizophrenia through founder effects.

Dr. Dohan also suggests that the high correlation between rates of wheat and rye consumption and first-admission rates for patients with schizophrenia provides additional support for his model. However, since these observations were made during World War II, the recognized effect of times of hardship on patterns of treatment for psychopathology should be borne in mind.

Finally, we take issue with Dr. Dohan's assertion that his hypothesis, even if corroborated, would provide an adequate etiologic explanation for schizophrenia in the "majority" of cases. Undoubtedly, schizophrenia, as a complex disease, may be caused by a variety of genetic as well as nongenetic factors (2). Dr. Dohan has no data bearing on the relative proportion of patients to whom the exorphin hypothesis might apply.

As Dr. Dohan himself has pointed out (3), the findings of studies of gluten-free diets are by no means incontrovertible. There have been two sizable studies in which a cereal-free, milk-free diet was helpful to patients with schizophrenia, but there have been three studies in which it was not.

All evidence of potential permissive—or protective—factors in schizophrenia should be examined closely. In our view, the majority of evidence to date has not supported the hypothesis that exorphins and gluten intolerance play a contributing role, although the hypothesis might profitably be studied further.

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Historical Note on an Unusual Tattoo

SIR: Several months ago I treated a male patient who had a tattoo around his neck like a "dog tag," which consisted of a dotted line with an inscription on his chest that stated, "Cut on dotted line." The tattoo seemed unique, and was consistent with the bravado of this Vietnam veteran, who was also a mercenary soldier. (He fortunately was not being treated for a neck wound but for substance abuse!)

I was surprised recently to come across a historical note on a similar tattoo: "I am reminded here of a story of a French murderer who had been sentenced to die on the guillotine. When he was prepared for execution, a dotted line was found tattooed on his neck, with, a little below, the words, 'Please cut on the dotted line' " (1, p. 184). Plus ça change, plus c'est la même chose!

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Corrections

In the article "Psychiatric Aspects of Organ Transplantation" (August 1989 issue, pp. 972–982) by Owen S. Surman, M.D., C.M., on p. 978, under Postoperative Adjustment, the second sentence should read, "The liver is relatively favored in this regard (133)."

In the review by Lyman C. Wynne, M.D., Ph.D., of the book *Marital and Family Therapy, 3rd ed.* by Ira D. Glick, M.D., John F. Clarkin, Ph.D., and David R. Kessler, M.D. (September 1989 issue, p. 1223), Drs. Glick, Clarkin, and Kessler should have been listed as authors of the book, not editors.

Reprints of letters to the Editor are not available.

Corporal Punishment in Schools

This statement was developed by Stephen P. Herman, M.D., for the Committee for Rights and Legal Matters[1] of the American Academy of Child and Adolescent Psychiatry, and it was approved by the American Academy of Child and Adolescent Psychiatry in June 1988. It was approved by the APA Assembly of District Branches in November 1988 and by the APA Board of Trustees in March 1989.

Corporal punishment is a method of discipline by which a supervising adult deliberately inflicts pain on a child in response to a child's unacceptable behavior and/or inappropriate language. The immediate aims of such punishment are usually to halt the offense, prevent its recurrence, and set an example for others. The purported long-term goal is to change the child's behavior and to make it more consistent with the adult's expectations. In corporal punishment, the adult usually hits various parts of the child's body with a hand or with a cane, paddle, yardstick, belt, or other object expected to cause pain and fear.

In the United States, 10 states explicitly bar corporal punishment in their schools: New York, New Jersey, Massachusetts, Vermont, Rhode Island, New Hampshire, Maine, Hawaii, Connecticut, and California. Certain large municipal school districts also prohibit this form of discipline: St. Louis, Atlanta, New Orleans, and Minneapolis. Similar legislation is pending in Ohio, Michigan, Wisconsin, and Alaska.

The American Academy of Child and Adolescent Psychiatry opposes the use of corporal punishment and supports legislation outlawing its use. Research on corporal punishment has shown that it may be harmful. Many other methods of discipline are effective in promoting self-control, eliminating undesirable behaviors, and promoting desired behaviors in children.

Corporal punishment signals to the child that a way to settle interpersonal conflicts is to use physical force and inflict pain. Such children may in turn resort to such behavior themselves. They may also fail to develop trusting, secure relationships with adults and fail to evolve the necessary skills to settle disputes or wield authority in less violent ways. Supervising adults who willfully humiliate children and punish by force and pain are often causing more harm than they prevent.

The American Academy of Child and Adolescent Psychiatry opposes the use of corporal punishment in schools and takes issue with laws in some states legalizing such corporal punishment and protecting adults who use it from prosecution for child abuse. The Academy joins with the National Congress of Parents and Teachers, the American Medical Association, the National Association of School Psychologists, the National Education Association, the American Bar Association, the American Academy of Pediatrics, and other groups calling for an end to this form of punishment.

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[1] The members of the American Academy of Child and Adolescent Psychiatry Committee for Rights and Legal Matters were Diane H. Schetky, M.D. (chairperson), John Sikorski, M.D. (cochairperson), Christine Adams, M.D., Elissa Benedek, M.D., Andre Derdeyn, M.D., Arthur Green, M.D., Elisabeth Lassers, M.D., Barry Nurcombe, M.D., Stepen Porter, M.D., and Stephen Herman, M.D. Outside consultants were David Chadwick, M.D., David Lloyd, J.D., Maria Sauzier, M.D., and Sue White, Ph.D.

The American Board of Psychiatry and Neurology, Inc.: Report on the April 1989 Examination

The following successfully completed the Board examination in April 1989.

PSYCHIATRY

Ackerley, Mary Beth, M.D., Owings Mills, MD
Adler, David Naftali, M.D., Lawrence, NY
Altman, Robert Michael, M.D., Alexandria, VA
Altshuler, Lori Lynn, M.D., Cabin John, MD
Amsel, Harold, M.D., New York, NY
Ang, Luis C., M.D., New York, NY
Arnold, Edward Stanley, M.D., Nashville, TN

Barris, Madeleine R., M.D., Bronx, NY
Behar, Lonny J., M.D., New York, NY
Bernstein, Beth Anne, M.D., Salt Lake City, UT
Bharatiya, Purabi, M.D., Scotch Plains, NJ
Blank, Susan Gail, M.D., Metuchen, NJ
Brandt, Harry Andrew, M.D., Baltimore, MD
Brown, Keith A., M.D., Bellevue, WA
Burciaga, Raul Rodolfo, M.D., Indianapolis, IN

Cabrero, Andres Tomas, M.D., New York, NY
Calabrese, Joseph Richard, M.D., Shaker Heights, OH
Call, Pamela Ullman, M.D., New York, NY
Callaghan, Marian Patricia, M.D., Marlton, NJ
Campo-Bowen, Ana Elisa, M.D., Coral Gables, FL
Cancellieri, Frank Remo, M.D., Brooklyn, NY
Capobianco, Francis Joseph, M.D., San Diego, CA
Cervantes, John Alexander, M.D., Ventura, CA
Chou, James C-Y, M.D., Orangeburg, NY
Cobert, Josiane Claude, M.D., Westfield, NJ
Cody, Mary Ellen, M.D., Baltimore, MD
Cohen, Howard Jay, M.D., Alexandria, VA
Compton, Alan Bertrand, M.D., Silver Spring, MD
Conant-Norville, David Oliver, M.D., Pendleton, OR
Cooper, Steven Jay, M.D., Monsey, NY
Corke, Patricia Perry, M.D., Houston, TX
Costanzo, Michael Francis, M.D., Katonah, NY
Cutler, Janis Lynne, M.D., New York, NY

Davis, Charles Talcott, M.D., New York, NY
DeAlwis, Jayakanthi, M.D., Short Hills, NJ
DeFrate, John Austin, M.D., Crownsville, MD
DeRitter, Lois May, M.D., Middlesex, NJ
Dech, Bert Ludig, M.D., Port Washington, NY
Dowling, Anthony Joseph, M.D., Warwick, RI
Downs, John McCall, M.D., Memphis, TN
Duncan, Erica Joan, M.D., New York, NY
Durruthy, Stephanie Susan, M.D., Columbia, MD

Egan, Michael Frederick, M.D., Chevy Chase, MD
Elfenbein, Cherie I., M.D., Staten Island, NY
Epstein, Mark David, M.D., New York City, NY

Fabian, Christopher A., M.D., New York, NY
Feld, Stephen, M.D., New York, NY
Felix, Alan David, M.D., New York, NY
Fine, Jeffrey Scott, M.D., New York, NY
First, Michael Bruce, M.D., New York City, NY
Fisher, Stephen, M.D., Oakland, CA
Flaum, Michael Alan, M.D., Iowa City, IA
Fox, Lewis Andrew, M.D., New York City, NY
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Freedman, Jeffrey Bruce, M.D., Bronx, NY
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INDICATIONS: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATED: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

WARNINGS: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

PRECAUTIONS: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

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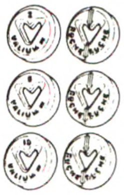

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Authors should use the active voice and first person; headings and subheadings should be inserted at reasonable intervals. Footnotes to text may not be used, and summaries are usually unnecessary.

Research design and statistics. The following information regarding research design should be included: 1) a clearly stated hypothesis, 2) the names of the statistical tests used, 3) whether tests were one- or two-tailed, and 4) what test was used for each set of data. Reporting of standard deviations, rather than standard errors of the mean, is required. Statistical tests that are not well known should be referenced. **All** significant and important nonsignificant results must include the test value, degree(s) of freedom, and probability. For example, "The analysis of variance indicated that those who abstained from coffee had significantly higher course grades than those who did not abstain ($F=4.32$, $df=3, 17$, $p<0.05$)." Reviewers will evaluate the appropriateness of the analyses.

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Drugs. Generic rather than trade names of drugs should be used. Trade or manufacturers' names are used only if the drug or equipment is experimental or unavailable in this country or if such information is crucial to the evaluation of the results or replication of the study.

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1. Noyes R Jr, DuPont RL Jr, Pecknold JC, et al: Alprazolam in panic disorder and agoraphobia, results from a multicenter trial, II: patient acceptance, side effects, and safety. Arch Gen Psychiatry 1988; 45:423–428
2. Kaplan HI, Sadock BJ (eds): Comprehensive Textbook of Psychiatry, 4th ed, vol 2. Baltimore, Williams & Wilkins, 1985
3. Fyer AJ, Manuzza S, Endicott J: Differential diagnosis and assessments of anxiety: recent developments, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven Press, 1987

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Tables should be double-spaced, no wider than 120 typewriter characters, including spaces, and no longer than 70 lines. Values expressed in the same unit of measurement should read down, not across; when percentages are given, the appropriate numbers must also be given.

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Format. Figures are visual expressions of data trends or relationships. Figures that represent numerical data which could be expressed more succinctly or clearly in tabular form should be converted to tables. Line graphs should show change in continuous variables; comparisons of like values in different groups should be presented as bar graphs. Graphs containing stacked bars are unacceptable; the different segments of each bar should be presented side by side.

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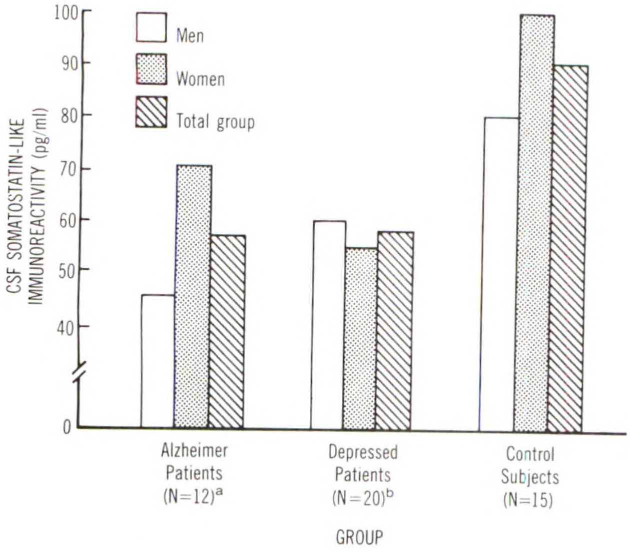
FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects



[a] Significant difference between men and women ($t=1.81$, $df=10$, $p<0.05$) and between the total Alzheimer's disease group and the total control group ($t=2.49$, $df=25$, $p<0.01$).

[b] Significant difference between the total depressed group and the total control group ($t=2.75$, $df=33$, $p<0.005$).

cient, headings may be placed diagonally on the axis. Main headings should consist of upper-case letters only, subheadings of upper- and lower-case, and other type (e.g., keys, flow chart segments) of lower-case with only an initial upper-case letter. All parenthetical material should be lower-case. Do not use idiosyncratic abbreviations.

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5. The vertical axis should generally begin at zero; to save space, a double slash may take the place of an unused portion of the vertical axis.
6. In a graph comparing different groups of subjects, the number of subjects in each group should appear with the name of the group—in the key, in the headings below the horizontal axis, or in the title.
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THORAZINE®
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See complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Contraindications: Comatose states or presence of large amounts of C.N.S. depressants.

Warnings: The possibility of extrapyramidal reactions from chlorpromazine may confuse the diagnosis of Reye's syndrome or other encephalopathy. Therefore, avoid use in children or adolescents with suspected Reye's syndrome.

May cause persistent tardive dyskinesia, which appears to be irreversible in some patients. Reserve chronic neuroleptic treatment for patients with chronic illness 1) that is known to respond to neuroleptics and 2) for whom there are no safer but equally effective treatment options. Use the smallest effective dose over the shortest treatment duration. If signs and symptoms of tardive dyskinesia develop, consider discontinuing the neuroleptic. A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. To manage NMS 1) discontinue immediately antipsychotic drugs and any other drugs not essential to concurrent therapy; 2) treat symptoms intensively and monitor; 3) where possible, treat serious concomitant medical problems. If antipsychotic treatment is needed after recovery from NMS, consider reintroducing drug therapy and monitor the patient carefully as recurrences of NMS have been reported. 'Thorazine' ampuls and vials contain sodium bisulfite and sodium sulfite; the sulfite may cause allergic reactions, including anaphylactic symptoms. In patients with bone marrow depression or previously demonstrated hypersensitivity (e.g., blood dyscrasias, jaundice) with phenothiazines, do not administer 'Thorazine' unless the potential treatment benefits outweigh the possible hazards. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days therapy. Avoid concomitant use with alcohol. May counteract antihypertensive effect of guanethidine and related compounds. Use in pregnancy only when essential. There are reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborns whose mothers had received chlorpromazine. Chlorpromazine is excreted in the breast milk of nursing mothers.

Precautions: Advise patients and/or guardians of the risk of tardive dyskinesia from chronic therapy. Use cautiously in persons with cardiovascular, liver, renal or chronic respiratory disease, or with acute respiratory infections. Patients with a history of hepatic encephalopathy due to cirrhosis have increased sensitivity to the C.N.S. effects of chlorpromazine. Due to cough reflex suppression, aspiration of vomitus is possible. May prolong or intensify the action of C.N.S. depressants, organophosphorus insecticides, heat, atropine and related drugs. (Reduce dosage of concomitant C.N.S. depressants.) Anticonvulsant action of barbiturates is not intensified.

Neuroleptic drugs cause elevated prolactin levels that persist during chronic administration. Since approximately one third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug administration is contemplated in a patient with a previously detected breast cancer. Neither clinical nor epidemiologic studies to date, however, have shown an association between the chronic administration of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in glaucoma patients. May diminish the effect of oral anticoagulants, produce α-adrenergic blockade, and lower the convulsive threshold; dosage adjustment of anticonvulsants may be required. May interfere with Dilantin®* metabolism, causing 'Dilantin' toxicity. May cause false positive phenylketonuria test results. Do not use with Amipaque®†. Discontinue 'Thorazine' at least 48 hours before myelography, do not resume for at least 24 hours postprocedure, and do not use to control N/V prior to myelography or postprocedure with 'Amipaque'. Evaluate patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics periodically to decide whether the dosage could be reduced or therapy discontinued. Antiemetic effect may mask signs of overdosage of other drugs or obscure diagnosis and treatment of conditions such as intestinal obstruction, brain tumor and Reye's syndrome (see Warnings). When used concomitantly, may obscure vomiting as a sign of toxicity of a cancer chemotherapeutic agent. Discontinue high-dose, long-term therapy gradually. Patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics should be evaluated periodically for possible adjustment or discontinuance of drug therapy.

Adverse Reactions: Drowsiness; cholestatic jaundice; agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, aplastic anemia, thrombocytopenic purpura and pancytopenia; postural hypotension, tachycardia, fainting, dizziness and occasionally a shock-like condition; reversal of epinephrine effects; EKG changes have been reported; neuromuscular (extrapyramidal) reactions: dystonias, motor restlessness, pseudo-parkinsonism, persistent tardive dyskinesia, psychotic symptoms, catatonic-like states, cerebral edema; convulsive seizures; abnormality of the cerebrospinal fluid proteins; urticarial reactions and photosensitivity, exfoliative dermatitis, contact dermatitis; asthma, laryngeal edema, angioneurotic edema, and anaphylactoid reactions; lactation and breast engorgement (in females on large doses), false positive pregnancy tests, amenorrhea, gynecomastia; hyperglycemia, hypoglycemia, glycosuria; dry mouth, nasal congestion, constipation, adynamic ileus, urinary retention, priapism, miosis, mydriasis; after prolonged substantial doses, skin pigmentation, epithelial keratopathy, lenticular and corneal deposits and pigmentary retinopathy, visual impairment; mild fever (after large I.M. doses); hyperpyrexia; increased appetite and weight; a systemic lupus erythematosus-like syndrome; peripheral edema.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported but no causal relationship has been established.

How Supplied: Tablets: 10 mg, 25 mg or 50 mg, in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 100 mg and 200 mg, in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only).

Spansule® brand of sustained release capsules: 30 mg, 75 mg, 150 mg or 200 mg, in bottles of 50 and 500; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 300 mg, in bottles of 50; in Single Unit Packages of 100 (intended for institutional use only).

Ampuls: 1 mL and 2 mL (25 mg/mL), in boxes of 10, 100 and 500.

Multiple-dose Vials: 10 mL (25 mg/mL), in boxes of 1, 20 and 100.

Syrup: 10 mg/5 mL in 4 fl oz bottles.

Suppositories: 25 mg or 100 mg, in boxes of 12.

Concentrate: Intended for institutional use. 30 mg/mL, in 4 fl oz bottles and in cartons of 36 bottles. 100 mg/mL, in 8 fl oz bottles, in cartons of 12.

*phenytoin, Parke-Davis.
†metrizamide, Winthrop Pharmaceuticals.

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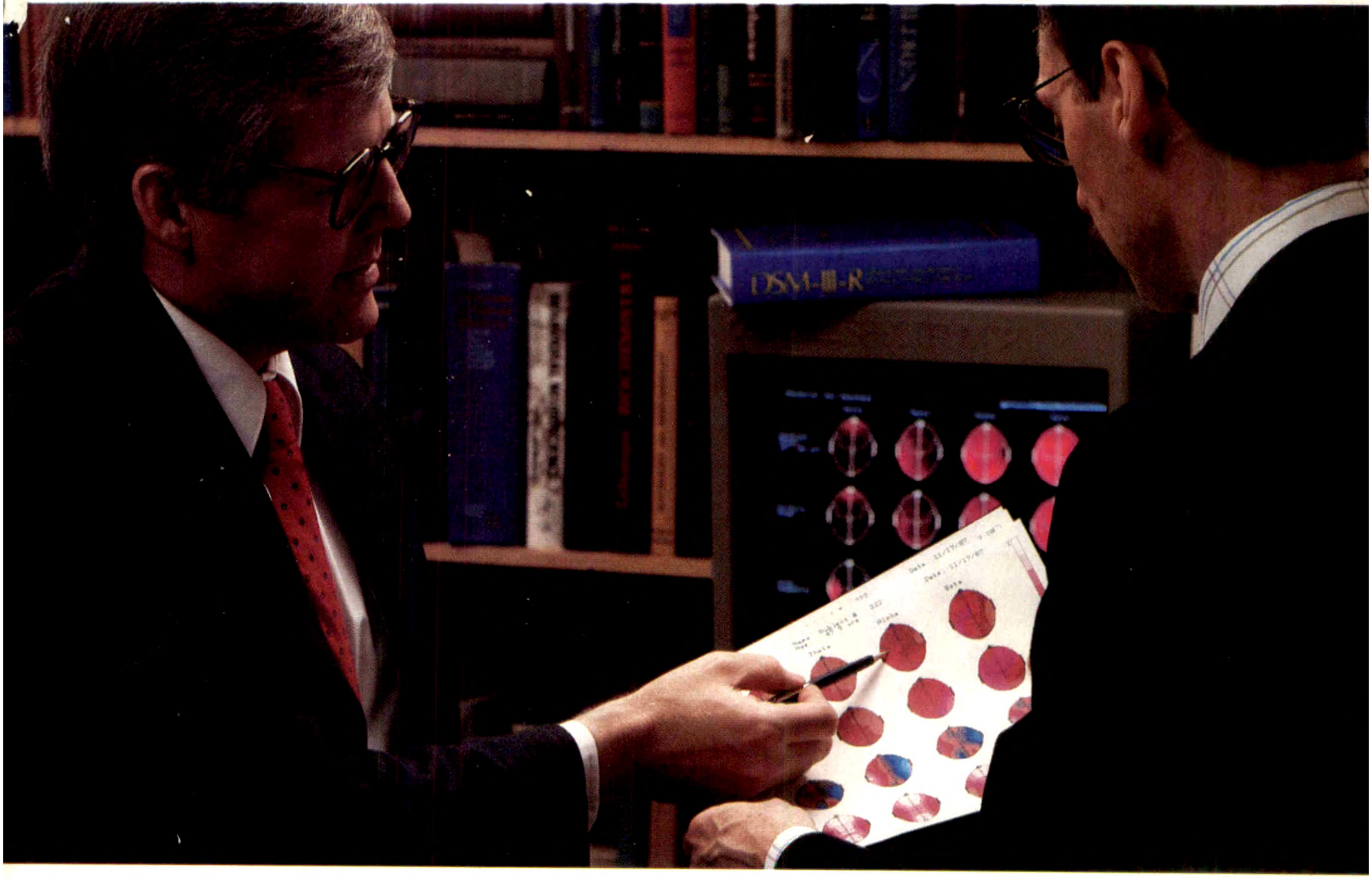

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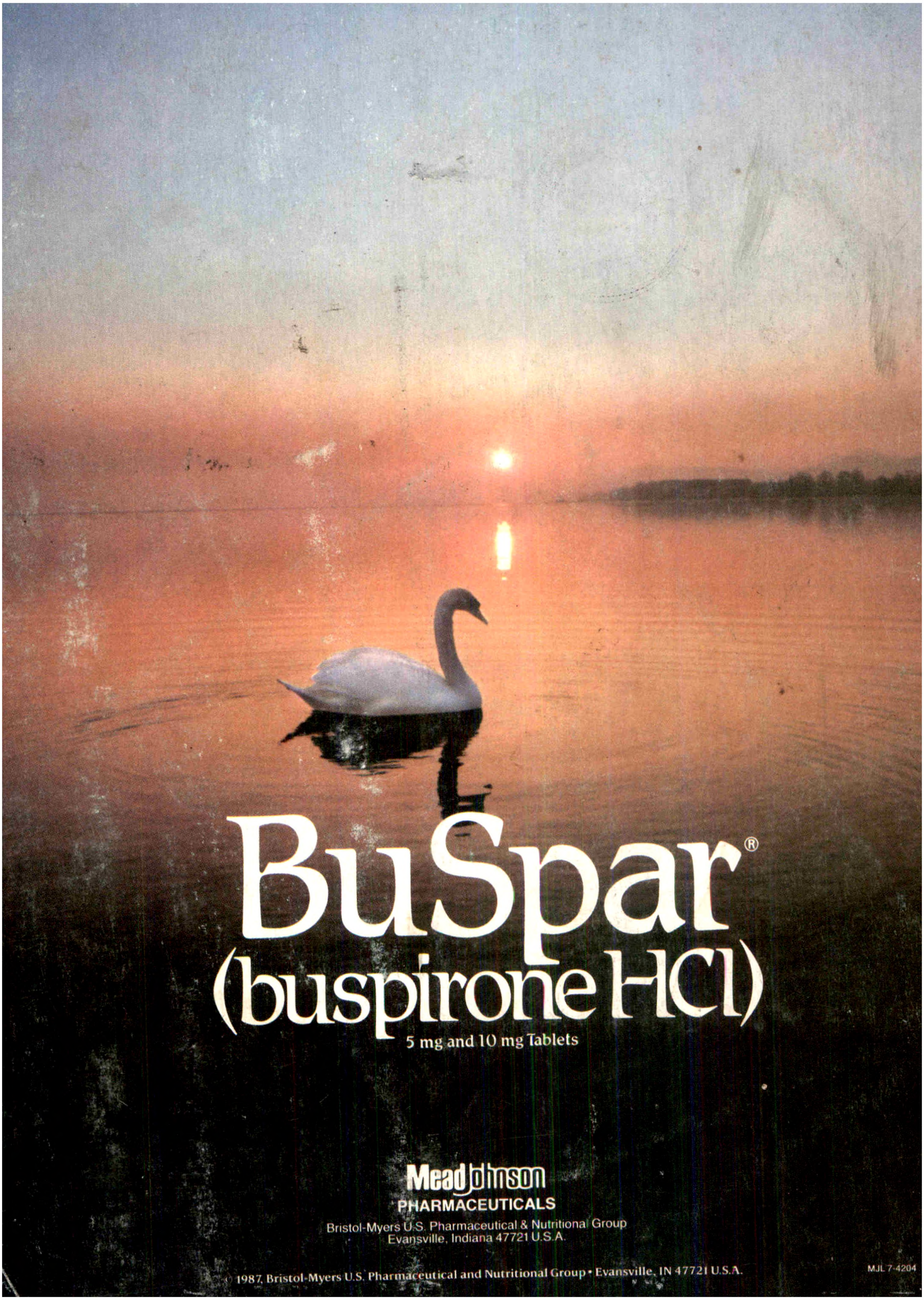

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